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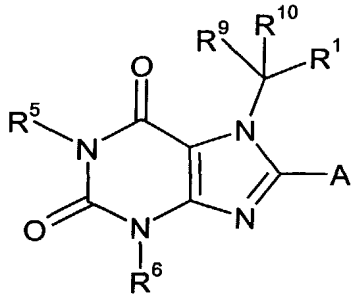
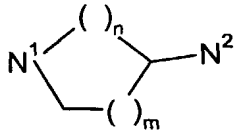
(54) Title: SUCCINATE SALTS OF HETEROCYCLIC DPP-IV INHIBITORS



A = 

(I)

(57) Abstract: The present invention relates to therapeutically active and selective hemisuccinate salts of inhibitors of the enzyme DPP-IV of formula (I), pharmaceutical compositions comprising the salts and the use of such salts for and the manufacture of medicaments for treating diseases that are associated with proteins that are subject to inactivation by DPP-IV, such as type 2 diabetes and obesity.

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SUCCINATE SALTS OF HETEROCYCLIC DPP-IV INHIBITORS

FIELD OF THE INVENTION

The present invention relates to therapeutically active and selective hemisuccinate salts of inhibitors of the enzyme DPP-IV, pharmaceutical compositions comprising the salts and the use of such salts for and the manufacture of medicaments for treating diseases that are associated with proteins that are subject to inactivation by DPP-IV, such as type 2 diabetes and obesity.

BACKGROUND OF THE INVENTION

Dipeptidyl peptidase-IV (DPP-IV), a serine protease belonging to the group of post-proline/alanine cleaving amino-dipeptidases, specifically removes the two N-terminal amino acids from proteins having proline or alanine in position 2.

Although the physiological role of DPP-IV has not been completely established, it is believed to play an important role in neuropeptide metabolism, T-cell activation, gastric ulceration, functional dyspepsia, obesity, appetite regulation, impaired fasting glucose (IFG) and diabetes.

DPP-IV has been implicated in the control of glucose metabolism because its substrates include the insulinotropic hormones Glucagon like peptide-1 (GLP-1) and Gastric inhibitory peptide (GIP). GLP-1 and GIP are active only in their intact forms, removal of their two N-terminal amino acids inactivates them.

In vivo administration of synthetic inhibitors of DPP-IV prevents N-terminal degradation of GLP-1 and GIP, resulting in higher plasma concentrations of these hormones, increased insulin secretion and, therefore, improved glucose tolerance. Therefore, such inhibitors have been proposed for the treatment of patients with Type 2 diabetes, a disease characterised by decreased glucose tolerance. (Holst, J. J., Deacon, C. F. Diabetes 47 (1998) 1663-70)

Diabetic dyslipidemia is characterized by multiple lipoprotein defects, including moderately high serum levels of cholesterol and triglycerides, small LDL particles, and low levels of HDL cholesterol. The results of recent clinical trials reveal beneficial effects of cholesterol-lowering therapy in diabetic and non-diabetic patients, thus supporting increased emphasis on treatment of diabetic dyslipidemia. The National Cholesterol Education Program's Adult Treatment Panel II advocated this need for intensive treatment of diabetic dyslipidemia.

Obesity is a well-known risk factor for the development of many very common diseases such as atherosclerosis, hypertension and diabetes. The incidence of obese people and thereby also these diseases is increasing throughout the entire industrialised world. Except for exercise, diet and food restriction no convincing pharmacological treatment for reducing body weight effectively and acceptably currently exist. However, due to its indirect but important effect as a risk factor in mortal and common diseases it will be important to find treatment for obesity or appetite regulation. Even mild obesity increases the risk for premature death, diabetes, hypertension, atherosclerosis, gallbladder disease and certain types of cancer. In the industrialised western world the prevalence of obesity has increased significantly in the past few decades. Because of the high prevalence of obesity and its health consequences, its prevention and treatment should be a high public health priority.

At present a variety of techniques are available to effect initial weight loss. Unfortunately, initial weight loss is not an optimal therapeutic goal. Rather, the problem is that most obese patients eventually regain their weight. An effective means to establish and/or sustain weight loss is the major challenge in the treatment of obesity today.

Several compounds have been shown to inhibit DPP-IV, but all of these have limitations in relation to the potency, stability, selectivity, toxicity, and pharmacodynamic properties. Thus, there is a need for the provision of DPP-IV inhibitors that are superior with respect to one or more of the above listed properties, and which will be useful for the treatment of conditions, which may be regulated or normalised by inhibition of DPP-IV. Furthermore, for commercial use it is important to have a physiologically acceptable salt with good stability, good solubility, non-hygroscopicity, good bioavailability, and good handling properties, like high melting point and a reproducible crystalline form.

Hydrochloride and trifluoroacetic acid salts of purine derivatives, attached at position 8 of the purine skeleton to a cyclic diamine, have previously been disclosed in PCT application PCT/DK02/00439. The trifluoracetic acid salts have undesirable pharmacologic properties, while the hydrochloric acid salts disclosed in PCT/DK02/00439 have been shown to have unfavourable properties with relation to crystalline forms. Furthermore, the powder properties of the hydrochloric acid salts disclosed in PCT/DK02/00439 make them unsuitable for handling in a large scale tabletting operation.

SUMMARY OF THE INVENTION

The present invention consists of hemisuccinate salts of purine derivatives, attached at position 8 of the purine skeleton to a cyclic diamine, at either one or the other of the amino

groups of the diamine. These salts are potent and selective inhibitors of DPP-IV, and are effective in treating conditions that may be regulated or normalised via inhibition of DPP-IV. The invention also concerns methods for preparing the salts, pharmaceutical compositions comprising the salts, a method of inhibiting DPP-IV comprising administering to a patient in need of such treatment a therapeutically effective amount of the salts of the invention, the salts for use as a pharmaceutical, and their use in a process for the preparation of a medicament for treating a condition which may be regulated or normalised via inhibition of DPP-IV.

DEFINITIONS

The term " DPP-IV" as used herein is intended to mean Dipeptidyl peptidase IV (EC 3.4.14.5, DPP-IV), also known as CD26. DPP-IV cleaves a dipeptide from the N terminus of a polypeptide chain containing a proline or alanine residue in the penultimate position.

The term "treatment" is defined as the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of hemisuccinate salt of a compound of the present invention to prevent the onset of the symptoms or complications, or alleviating the symptoms or complications, or eliminating the disease, condition, or disorder.

The term "beta cell degeneration" is intended to mean loss of beta cell function, beta cell dysfunction, and death of beta cells, such as necrosis or apoptosis of beta cells.

The term "C_1-C_{10} alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated hydrocarbon chain having from 1-10 carbon atoms such as but not limited to e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec. Butyl, isobutyl, tert. Butyl, n-pentyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, 4-methylpentyl, neopentyl, 2,2-dimethylpropyl and the like.

The term "C_2-C_{10}-alkenyl" used herein, alone or in combination, refers to a straight or branched, unsaturated hydrocarbon chain having from 2-10 carbon atoms and at least one double bond such as but not limited to vinyl, 1-propenyl, allyl, isopropenyl, n-butenyl, n-pentenyl and n-hexenyl and the like.

The term "C_2-C_{10} alkynyl" as used herein, alone or in combination, refers to an unsaturated hydrocarbon chain having from 2-10 carbon atoms and at least one triple bond such as but not limited to -C≡CH, -C≡CCH_3, -CH_2C≡CH, -CH_2-CH_2-C≡CH, -CH(CH_3)C≡CH and the like.

The term "C_1-C_{10}-alkoxy" as used herein, alone or in combination is intended to include those C_1-C_{10}-alkyl groups of the designated length in either a linear or branched or cyclic con-

figuration linked through an ether oxygen having its free valence bond from the ether oxygen. Examples of linear alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy. Examples of branched alkoxy are isopropoxy, sec-butoxy, tert-butoxy, isopentoxy and isohexoxy. Examples of cyclic alkoxy are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

The term "C_3-C_{10} cycloalkyl" as used herein refers to a radical of one or more saturated cyclic hydrocarbon having from 3-10 carbon atoms such as but not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl and the like.

The term "C_3-C_{10} cycloalkane" as used herein refers to a saturated cyclic hydrocarbon having from 3-10 carbon atoms such as but not limited to cyclopropane, cyclobutane, cyclopentane, cyclohexane, adamantane and the like.

The term "C_5-C_{10} cycloalkenyl" as used herein refers to a radical of one or more cyclic hydrocarbon having at least one double bond having from 5-10 carbon atoms such as but not limited to cyclopentenyl, cyclohexenyl and the like

The term "C_3-C_7 cycloheteroalkyl" as used herein refers to a radical of totally saturated heterocycle like a cyclic hydrocarbon containing one or more heteroatoms selected from nitrogen, oxygen and sulphur independently in the cycle such as pyrrolidine (1- pyrrolidine, 2- pyrrolidine, 3- pyrrolidine, 4- pyrrolidine, 5- pyrrolidine), pyrazolidine (1- pyrazolidine, 2- pyrazolidine, 3- pyrazolidine, 4-pyrazolidine, 5-pyrazolidine), imidazolidine (1-imidazolidine, 2- imidazolidine, 3- imidazolidine, 4- imidazolidine, 5- imidazolidine), thiazolidine (2- thiazolidine, 3- thiazolidine, 4- thiazolidine, 5- thiazolidine), piperidine (1-piperidine, 2- piperidine, 3- piperidine, 4- piperidine, 5- piperidine, 6- piperidine), piperazine (1- piperazine, 2- piperazine, 3- piperazine, 4- piperazine, 5- piperazine, 6- piperazine), morpholine (2- morpholine, 3- morpholine, 4- morpholine, 5- morpholine, 6- morpholine), thiomorpholine (2- thiomorpholine, 3- thiomorpholine, 4- thiomorpholine, 5- thiomorpholine, 6-thiomorpholine), 1,2-oxathiolane (3-(1,2-oxathiolane), 4-(1,2-oxathiolane), 5-(1,2-oxathiolane), 1,3-dioxolane (2-(1,3-dioxolane), 4-(1,3-dioxolane), 5-(1,3-dioxolane), tetrahydropyrane, (2-tetrahydropyrane, 3-tetrahydropyrane, 4-tetrahydropyrane, 5-tetrahydropyrane, 6-tetrahydropyrane), hexahydropyridazine (1-(hexahydropyridazine), 2-(hexahydropyridazine), 3-(hexahydropyridazine), 4-(hexahydropyridazine), 5-(hexahydropyridazine), 6-(hexahydropyridazine)).

The term "aryl" as used herein includes carbocyclic aromatic ring systems. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems.

The term "heteroaryl" as used herein includes heterocyclic unsaturated ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulphur such as

furyl, thienyl, pyrrolyl, heteroaryl is also intended to include the partially hydrogenated derivatives of the heterocyclic systems enumerated below.

The terms "aryl" and "heteroaryl" as used herein refers to an aryl which can be optionally substituted or a heteroaryl which can be optionally substituted and includes phenyl, biphenyl, indenyl, naphthyl (1-naphthyl, 2-naphthyl), N-hydroxytetrazolyl, N-hydroxytriazolyl, N-hydroxyimidazolyl, anthracenyl (1-anthracenyl, 2-anthracenyl, 3-anthracenyl), thiophenyl (2-thienyl, 3-thienyl), furyl (2-furyl, 3-furyl), indolyl, oxadiazolyl, isoxazolyl, quinazolinyl, fluorenyl, xanthenyl, isoindanyl, benzhydryl, acridinyl, thiazolyl, pyrrolyl (2-pyrrolyl), pyrazolyl (3-pyrazolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3- pyridazinyl, 4-pyridazinyl, 5-pyridazinyl), quinolyl (2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), isoquinolyl (1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), benzo[b]furanyl (2-benzo[b]furanyl, 3-benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl), 2,3-dihydro-benzo[b]furanyl (2-(2,3-dihydro-benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl), 4-(2,3-dihydro-benzo[b]furanyl), 5-(2,3-dihydro-benzo[b]furanyl), 6-(2,3-dihydro-benzo[b]furanyl), 7-(2,3-dihydro-benzo[b]furanyl), benzo[b]thiophenyl (2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl, 7-benzo[b]thiophenyl), 2,3-dihydro-benzo[b]thiophenyl (2-(2,3-dihydro-benzo[b]thiophenyl), 3-(2,3-dihydro-benzo[b]thiophenyl), 4-(2,3-dihydro-benzo[b]thiophenyl), 5-(2,3-dihydro-benzo[b]thiophenyl), 6-(2,3-dihydro-benzo[b]thiophenyl), 7-(2,3-dihydro-benzo[b]thiophenyl), indolyl (1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), indazole (1-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl), benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoxazolyl (1-benzoxazolyl, 2-benzoxazolyl), benzothiazolyl (1-benzothiazolyl, 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), carbazolyl (1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), 5H-dibenz[b,f]azepine (5H-dibenz[b,f]azepin-1-yl, 5H-dibenz[b,f]azepine-2-yl, 5H-dibenz[b,f]azepine-3-yl, 5H-dibenz[b,f]azepine-4-yl, 5H-dibenz[b,f]azepine-5-yl), 10,11-dihydro-5H-dibenz[b,f]azepine (10,11-dihydro-5H-dibenz[b,f]azepine-1-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-2-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-3-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-4-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-5-yl).

The term "halogen" as used herein refers to fluoro, chloro, bromo, and iodo.

The term "aryl-C_1-C_5 alkyl" as used herein refers to an "aryl" group as defined above attached through an "alkyl" group as defined above having the indicated number of carbon atoms.

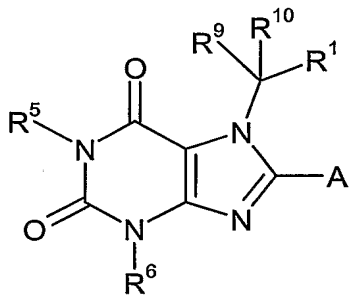
The term "heteroaryl-C_1-C_5 alkyl" as used herein refers to a "heteroaryl" group as defined above attached through an "alkyl" group as defined above having the indicated number of carbon atoms.

The term "C_3-C_7 cycloalkyl-C_1-C_5 alkyl" as used herein refers to a "cycloalkyl" group as defined above having the indicated number of carbon atoms attached through an "alkyl" group as defined above having the indicated number of carbon atoms.

The term "C_3-C_7 cycloheteroalkyl-C_1-C_5 alkyl" as used herein refers to a "cycloheteroalkyl" group as defined above having the indicated number of carbon atoms attached through an "alkyl" group as defined above having the indicated number of carbon atoms.

DESCRIPTION OF THE INVENTION

The present invention provides hemisuccinate salts of the compounds of formula I



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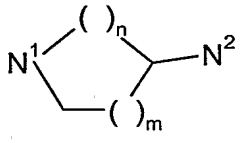


Formula I

wherein A may be attached at either N^1 or at N^2 to the purine system and each n and m is one or two independently

R^1 is aryl optionally substituted with one or more R^2 independently or heteroaryl optionally substituted with one or more R^2 independently,

R^2 is H, C_1-C_7 alkyl, C_2-C_7 alkenyl, C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, -$NHCOR^3$, -$NHSO_2R^3$, -SR^3, -SOR^3, -SO_2R^3, -$OCOR^3$, -CO_2R^4, -$CON(R^4)_2$, -$CSN(R^4)_2$, -$NHCON(R^4)_2$, -$NHCSN(R^4)_2$, -$NHCONNH_2$, -$SO_2N(R^4)_2$, -OR^4, cyano, nitro, halogen, wherein each alkyl, alkenyl, alkynyl, cycloalkyl and cycloheteroalkyl is optionally substituted with one or more R^3 independently,

R^3 is Halogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_7 cycloalkyl, aryl, heteroaryl, -OR^{11}, -$N(R^{11})_2$, -SR^{11}, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl is substituted with one or more R^{11} independently,

R^4 is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, aryl-C_1-C_5 alkyl, heteroaryl, heteroaryl-C_1-C_5 alkyl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, aryl-C_1-C_5 alkyl, heteroaryl, and heteroaryl-C_1-C_5 alkyl is substituted with one or more R^{11} independently,

R^5 is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl-C_1-C_5 alkyl, C_3-C_7 cycloheteroalkyl, C_3-C_7 cycloheteroalkyl-C_1-C_5 alkyl, aryl, heteroaryl,

aryl-C_1-C_5 alkyl, heteroaryl-C_1-C_5 alkyl, -OR^7, -$[(CH_2)_o$-$O]_p$-alkyl, wherein o and p are 1-3 independently, and wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-C_1-C_5 alkyl, cycloheteroalkyl, C_3-C_7 cycloheteroalkyl-C_1-C_5 alkyl, aryl, aryl-C_1-C_5 alkyl, heteroaryl, and heteroaryl-C_1-C_5 alkyl is optionally substituted with one or more substituents independently selected from R^7 or R^{11} independently,

R^6 is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, heteroaryl, aryl-C_1-C_5 alkyl, heteroaryl-C_1-C_5 alkyl, C_3-C_7 cycloheteroalkyl-C_1-C_5 alkyl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, C_3-C_7 cycloheteroalkyl-C_1-C_5 alkyl, aryl, aryl-C_1-C_5 alkyl, heteroaryl, aryl-C_1-C_5 alkyl, and heteroaryl-C_1-C_5 alkyl is optionally substituted with one or more R^{11} independently,

R^7 is H, =O, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, heteroaryl, -OR^{11}, -$N(R^{11})_2$, -SR^{11}, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, and heteroaryl is optionally substituted with one or more R^{11} independently,

R^8 is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, heteroaryl, -OR^{11}, -$N(R^{11})_2$, -SR^{11}, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, and heteroaryl is optionally substituted with one or more R^{11} independently,

R^9 and R^{10} is independently H, C_1-C_{10} alkyl optionally substituted with one or more R^8 independently, or halogen,

R^{11} is H, -CF_3, -CCl_3, -OCF_3, -OMe, cyano, halogen, -OH, -COMe, -$CONH_2$, -CONHMe, -$CONMe_2$, -NO_2, C_1-C_{10} alkyl, aryl, heteroaryl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, wherein each alkyl, cycloalkyl, cycloheteroalkyl, aryl, and heteroaryl is optionally substituted with one or more R^{12} independently,

R^{12} is H, C_1-C_{10} alkyl, -CF_3, -CCl_3, -OCF_3, -OMe, cyano, halogen, -OH, -COMe, -$CONH_2$, -CONHMe, -$CONMe_2$, -NH_2, -NO_2

If R^9 and R^{10} is C_1-C_{10} alkyl they may be connected to form a cyclopropyl ring,

if two R^4 or two R^{11} are attached to the same nitrogen they may be connected to form a 3- to 7-membered ring,

or any tautomeric form or any optical isomer or mixture of optical isomers, including a racemic mixture.

In a further embodiment of the invention R^1 is aryl optionally substituted with one or more R^2 independently.

In a further embodiment of the invention R^1 is phenyl substituted with one or more R^2 independently.

In a further embodiment of the invention R^1 is aryl.

In a further embodiment of the invention R^1 is phenyl.

In a further embodiment of the invention R^2 is C_1-C_7 alkyl, C_2-C_7 alkynyl, cyano, or halogen, wherein each alkyl and alkynyl is optionally substituted with one or more R^3 independently.

In a further embodiment of the invention R^2 is C_1-C_7 alkyl, C_2-C_7 alkynyl, cyano, or halogen.

In a further embodiment of the invention R^2 is methyl.

In a further embodiment of the invention R^2 is cyano or halogen.

In a further embodiment of the invention R^3 is C_1-C_{10} alkyl or aryl, wherein each alkyl or aryl is substituted with one or more R^{11} independently.

In a further embodiment of the invention R^3 is C_1-C_{10} alkyl or aryl.

In a further embodiment of the invention R^3 is methyl or phenyl.

In a further embodiment of the invention R^4 is H, C_1-C_{10} alkyl or aryl, wherein each alkyl or aryl is substituted with one or more R^{11} independently.

In a further embodiment of the invention R^4 is H, C_1-C_{10} alkyl or aryl.

In a further embodiment of the invention R^4 is H, methyl or phenyl.

In a further embodiment of the invention R^5 is H, C_1-C_{10} alkyl, aryl-C_1-C_5 alkyl, or heteroaryl-C_1-C_5 alkyl, wherein each alkyl, aryl-C_1-C_5 alkyl and heteroaryl-C_1-C_5 alkyl is optionally substituted with one or more R^7 independently.

In a further embodiment of the invention R^5 is H or C_1-C_{10} alkyl optionally substituted with one or more R^7 independently.

In a further embodiment of the invention R^5 is H or C_1-C_{10} alkyl.

In a further embodiment of the invention R^5 is H.

In a further embodiment of the invention R^5 is methyl.

In a further embodiment of the invention R^6 is C_1-C_{10} alkyl, aryl-C_1-C_5 alkyl, or heteroaryl-C_1-C_5 alkyl, wherein each alkyl, aryl-C_1-C_5 alkyl and heteroaryl-C_1-C_5 alkyl is optionally substituted with one or more R^{11} independently.

In a further embodiment of the invention R^6 is C_1-C_{10} alkyl, aryl-C_1-C_5 alkyl, or heteroaryl-C_1-C_5 alkyl.

In a further embodiment of the invention R^6 is C_1-C_{10} alkyl optionally substituted with one or more R^{11} independently.

In a further embodiment of the invention R^6 is C_1-C_{10} alkyl.

In a further embodiment of the invention R^6 is methyl.

In a further embodiment of the invention R^7 is H, =O, aryl, heteroaryl, OR^{11}, $N(R^{11})_2$, SR^{11}, wherein each aryl and heteroaryl is optionally substituted with one or more R^{11} independently.

In a further embodiment of the invention R^7 is H, =O, aryl, or heteroaryl.

In a further embodiment of the invention R^7 is H, =O, OR^{11}, $N(R^{11})_2$, or SR^{11}.

In a further embodiment of the invention R^7 is H or =O.

In a further embodiment of the invention R^8 is aryl or heteroaryl, wherein each aryl and heteroaryl is optionally substituted with one or more R^{11} independently.

In a further embodiment of the invention R^8 is aryl or heteroaryl.

In a further embodiment of the invention R^8 is phenyl.

In a further embodiment of the invention R^9 is H, C_1-C_{10} alkyl, or halogen.

In a further embodiment of the invention R^9 is H.

In a further embodiment of the invention R^{10} is H, C_1-C_{10} alkyl, or halogen.

In a further embodiment of the invention R^{10} is H.

In a further embodiment of the invention R^{11} is H, $-CF_3$, cyano, halogen, -OH, $-NO_2$, C_1-C_{10} alkyl, aryl, heteroaryl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, wherein each alkyl, cycloalkyl, cycloheteroalkyl, aryl, and heteroaryl is optionally substituted with one or more R^{12} independently

In a further embodiment of the invention R^{11} is H, halogen, -OH, C_1-C_{10} alkyl, aryl, heteroaryl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, wherein each alkyl, cycloalkyl, cycloheteroalkyl, aryl, and heteroaryl is optionally substituted with one or more R^{12} independently.

In a further embodiment of the invention R^{11} is H, halogen, $-CH_3$, aryl, heteroaryl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, wherein each alkyl, cycloalkyl, cycloheteroalkyl, aryl, and heteroaryl is optionally substituted with one or more R^{12} independently.

In a further embodiment of the invention R^{11} is H, halogen, $-CH_3$, heteroaryl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, wherein each alkyl, cycloalkyl, cycloheteroalkyl, and heteroaryl is optionally substituted with one or more R^{12} independently

In a further embodiment of the invention R^{11} is H, halogen, or $-CH_3$

In a further embodiment of the invention R^{11} is heteroaryl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, wherein each cycloalkyl, cycloheteroalkyl,and heteroaryl is optionally substituted with one or more R^{12} independently

In a further embodiment of the invention R^{11} is selected from the group consisting of pyridine, cyclopentane, cyclohexane, and pyrrolidine, wherein each cycloalkyl, cycloheteroalkyl, and heteroaryl is optionally substituted with one or more R^{12} independently

In a further embodiment of the invention R^{12} is H, C_1-C_{10} alkyl, $-CF_3$, cyano, halogen, -OH, -COMe, $-NH_2$, $-NO_2$

In a further embodiment of the invention R^{12} is H, $-CF_3$, cyano, halogen, -OH, $-NH_2$

In a further embodiment of the invention R^{12} is –OH or $-NH_2$

In a further embodiment of the invention n is two.

In a further embodiment of the invention n is one.

In a further embodiment of the invention m is two or three.

In a further embodiment of the invention m is two

In a further embodiment of the invention m is three

The hemisuccinate salts of the following compounds of Formula I are preferred:

2-(8-(3-Aminopiperidin-1-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl)benzonitrile.

8-(3-Aminopyrrolidin-1-yl)-7-benzyl-1,3-dimethyl-3,7-dihydropurine-2,6-dione.

(S) 8-(3-Aminopyrrolidin-1-yl)-7-benzyl-1,3-dimethyl-3,7-dihydropurine-2,6-dione.

2-(8-(3-Aminopyrrolidin-1-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl)benzonitrile.

8-(3-Aminopyrrolidin-1-yl)-7-(2-iodobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione.

8-(3-Aminoazepan-1-yl)-7-benzyl-1,3-dimethyl-3,7-dihydropurine-2,6-dione.

(S) 8-(3-Aminopyrrolidin-1-yl)-7-(2-iodobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione.

(S) 2-(8-(3-Aminopyrrolidin-1-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl)benzonitrile.

8-(3-Aminopiperidin-1-yl)-7-(2-iodobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione.

8-(3-Aminopiperidin-1-yl)-7-(2-bromobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione.

(R) 8-(3-Aminopyrrolidin-1-yl)-7-(2-bromobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione.

(S) 8-(3-Aminopyrrolidin-1-yl)-7-(2-bromobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione.

(R) 8-(3-Aminopyrrolidin-1-yl)-7-benzyl-1,3-dimethyl-3,7-dihydropurine-2,6-dione.

(R) 2-(8-(3-Aminopyrrolidin-1-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl)benzonitrile.

(R) 8-(3-Aminopyrrolidin-1-yl)-7-(2-iodobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione.

(R) 2-[8-(3-Aminopiperidin-1-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl]-benzonitrile.

(R) 8-(3-Aminopiperidin-1-yl)-7-benzyl-1,3-dimethyl-3,7-dihydropurine-2,6-dione.

(R) 8-(3-Aminopiperidin-1-yl)-1,3-dimethyl-7-(2-methylbenzyl)-3,7-dihydropurine-2,6-dione.

(R) 8-(3-Aminopiperidin-1-yl)-7-(2-chlorobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione.

(R) 8-(3-Aminopiperidin-1-yl)-7-(2-bromobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione.

(R) 8-(3-Aminopiperidin-1-yl)-7-(2-bromobenzyl)-3-methyl-1-(2-oxo-2-phenylethyl)-3,7-dihydro-purine-2,6-dione.

(R) 8-(3-Aminopiperidin-1-yl)-7-(2-bromobenzyl)-3-methyl-1-phenethyl-3,7-dihydropurine-2,6-dione.

(R) 8-(3-Aminopiperidin-1-yl)-7-(2-chlorobenzyl)-3-methyl-1-phenethyl-3,7-dihydropurine-2,6-dione.

(R) 2-[8-(3-Aminopiperidin-1-yl)-7-(2-chlorobenzyl)-3-methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-1-ylmethyl]benzonitrile

2-[8-(3-Aminopiperidin-1-yl)-7-(2-cyanobenzyl)-3-methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-1-ylmethyl]benzonitrile

(R) 2-[8-(3-Aminopiperidin-1-yl)-7-(2-cyanobenzyl)-3-methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-1-ylmethyl]benzonitrile.

(R) 2-[8-(3-(R)-Aminopiperidin-1-yl)-3-methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl]benzonitrile.

(R) 8-(3-Aminopiperidin-1-yl)-7-(2-chlorobenzyl)-3-methyl-3,7-dihydropurine-2,6-dione.

(R) 8-(3-Aminopiperidin-1-yl)-7-(2-bromobenzyl)-3-methyl-1-(2-oxo-2-thiophen-3-yl-ethyl)-3,7-dihydropurine-2,6-dione.

(R) 2-[8-(3-Aminopiperidin-1-yl)-3-methyl-2,6-dioxo-1-(2-oxo-2-thiophen-3-yl-ethyl)-1,2,3,6-tetrahydropurin-7-ylmethyl]benzonitrile.

8-(3-Amino-piperidin-1-yl)-3-benzyl-7-(3-fluoro-benzyl)-3,7-dihydro-purine-2,6-dione

8-(3-Amino-piperidin-1-yl)-3-benzyl-7-(2-chloro-benzyl)-3,7-dihydro-purine-2,6-dione

8-(3-Amino-piperidin-1-yl)-3-benzyl-7-(2-bromo-benzyl)-3,7-dihydro-purine-2,6-dione

8-(3-Amino-piperidin-1-yl)-3-benzyl-7-(2-methyl-benzyl)-3,7-dihydro-purine-2,6-dione

8-(3-Amino-piperidin-1-yl)-3,7-dibenzyl-3,7-dihydro-purine-2,6-dione

8-(3-Amino-piperidin-1-yl)-3-benzyl-7-(3,5-difluoro-benzyl)-3,7-dihydro-purine-2,6-dione
8-(3-Amino-piperidin-1-yl)-3-benzyl-7-(2,5-difluoro-benzyl)-3,7-dihydro-purine-2,6-dione
8-(3-Amino-piperidin-1-yl)-3-benzyl-7-(2-difluoromethoxy-benzyl)-3,7-dihydro-purine-2,6-dione
8-(3-Amino-piperidin-1-yl)-7-(3-fluoro-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione
8-(3-Amino-piperidin-1-yl)-7-(2-chloro-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione
8-(3-Amino-piperidin-1-yl)-3-methyl-7-(2-methyl-benzyl)-3,7-dihydro-purine-2,6-dione
8-(3-Amino-piperidin-1-yl)-7-benzyl-3-methyl-3,7-dihydro-purine-2,6-dione
8-(3-Amino-piperidin-1-yl)-7-(3,5-difluoro-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione
8-(3-Amino-piperidin-1-yl)-7-(3-fluoro-benzyl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione
8-(3-Amino-piperidin-1-yl)-1,3-dimethyl-7-(2-methyl-benzyl)-3,7-dihydro-purine-2,6-dione
8-(3-Amino-piperidin-1-yl)-7-(3,5-difluoro-benzyl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione
8-(3-Amino-piperidin-1-yl)-7-(2,5-difluoro-benzyl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione
8-(3-Amino-piperidin-1-yl)-7-(2-difluoromethoxy-benzyl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione
8-(3-Amino-piperidin-1-yl)-7-(2-chloro-benzyl)-3-methyl-1-(2-oxo-2-phenyl-ethyl)-3,7-dihydro-purine-2,6-dione
8-(R-3-Amino-piperidin-1-yl)-7-(2-chloro-benzyl)-3-methyl-1-(2-oxo-2-phenyl-ethyl)-3,7-dihydro-purine-2,6-dione
2-[8-(3-Aminopiperidin-1-yl)-7-(2-bromobenzyl)-3-methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-1-ylmethyl]benzonitrile
8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-3-methyl-1-(2-oxo-2-phenyl-ethyl)-3,7-dihydro-purine-2,6-dione
8-(3-Amino-piperidin-1-yl)-3-methyl-1-(2-oxo-2-phenyl-ethyl)-7-(2-trifluoromethyl-benzyl)-3,7-dihydro-purine-2,6-dione
8-(3-Amino-piperidin-1-yl)-1-(2-benzo[*b*]thiophen-3-yl-2-oxo-ethyl)-7-(2-chloro-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione
8-(3-Amino-piperidin-1-yl)-7-(2-chloro-benzyl)-1-[2-(3-fluoro-phenyl)-2-oxo-ethyl]-3-methyl-3,7-dihydro-purine-2,6-dione
8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-1-(2-cyclopropyl-2-oxo-ethyl)-3-methyl-3,7-dihydro-purine-2,6-dione
8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-1-[2-(2,6-dimethoxy-phenyl)-2-oxo-ethyl]-3-methyl-3,7-dihydro-purine-2,6-dione
8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-3-methyl-1-(2-oxo-2-thiophen-3-yl-ethyl)-3,7-dihydro-purine-2,6-dione

8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-1-[2-(4-chloro-phenyl)-2-oxo-ethyl]-3-methyl-3,7-dihydro-purine-2,6-dione

8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-3-methyl-1-(2-oxo-2-*p*-tolyl-ethyl)-3,7-dihydro-purine-2,6-dione

8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-1-[2-(2-chloro-phenyl)-2-oxo-ethyl]-3-methyl-3,7-dihydro-purine-2,6-dione

8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-1-[2-(3-methoxy-phenyl)-2-oxo-ethyl]-3-methyl-3,7-dihydro-purine-2,6-dione

8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-1-[2-(2-methoxy-phenyl)-2-oxo-ethyl]-3-methyl-3,7-dihydro-purine-2,6-dione

8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-3-methyl-1-(2-oxo-butyl)-3,7-dihydro-purine-2,6-dione

8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-3-methyl-1-(2-oxo-1-phenyl-pyrrolidin-3-yl)-3,7-dihydro-purine-2,6-dione

8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-1-[2-(3-chloro-phenyl)-2-oxo-ethyl]-3-methyl-3,7-dihydro-purine-2,6-dione

2-{8-(3-Amino-piperidin-1-yl)-1-[2-(2,6-difluoro-phenyl)-2-oxo-ethyl]-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-ylmethyl}-benzonitrile

2-[8-(3-Amino-piperidin-1-yl)-3-methyl-2,6-dioxo-1-(2-oxo-2-thiophen-3-yl-ethyl)-1,2,3,6-tetrahydro-purin-7-ylmethyl]-benzonitrile

2-[8-(3-Amino-piperidin-1-yl)-1-(2-benzo[*b*]thiophen-3-yl-2-oxo-ethyl)-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-ylmethyl]-benzonitrile

2-[8-(3-Amino-piperidin-1-yl)-3-methyl-2,6-dioxo-1-(2-oxo-2-phenyl-ethyl)-1,2,3,6-tetrahydro-purin-7-ylmethyl]-benzonitrile

2-{8-(3-Amino-piperidin-1-yl)-1-[2-(3-fluoro-phenyl)-2-oxo-ethyl]-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-ylmethyl}-benzonitrile

8-(3-Amino-piperidin-1-yl)-3-methyl-1-(2-oxo-2-phenyl-ethyl)-7-(3-trifluoromethoxy-benzyl)-3,7-dihydro-purine-2,6-dione

8-(3-Amino-piperidin-1-yl)-7-(2-fluoro-6-trifluoromethyl-benzyl)-3-methyl-1-(2-oxo-2-phenyl-ethyl)-3,7-dihydro-purine-2,6-dione

8-(3-Amino-piperidin-1-yl)-7-(2-fluoro-5-trifluoromethyl-benzyl)-3-methyl-1-(2-oxo-2-phenyl-ethyl)-3,7-dihydro-purine-2,6-dione

2-(8-(3-Aminoazepan-1-yl)-7-(2-chlorobenzyl)-3-methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-1-ylmethyl)benzonitrile.

8-(3-Aminoazepan-1-yl)-7-(2-chlorobenzyl)-3-methyl-3,7-dihydropurine-2,6-dione.

8-(3-Aminoazepan-1-yl)-7-benzyl-3-methyl-1-(2-oxo-2-phenylethyl)-3,7-dihydropurine-2,6-dione.

8-(3-Aminoazepan-1-yl)-7-benzyl-3-methyl-3,7-dihydropurine-2,6-dione.

2-(8-(3-Aminoazepan-1-yl)-3-methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl)benzonitrile.

8-(3-Aminoazepan-1-yl)-7-(2-bromobenzyl)-3-methyl-3,7-dihydropurine-2,6-dione.

8-(3-Aminoazepan-1-yl)-3-methyl-7-(2-trifluoromethylbenzyl)-3,7-dihydropurine-2,6-dione.

8-(3-Aminoazepan-1-yl)-3-methyl-7-(2-methylbenzyl)-3,7-dihydropurine-2,6-dione.

8-(3-Aminoazepan-1-yl)-7-(2-bromobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione.

2-[8-(3-Aminoazepan-1-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl]benzonitrile.

8-(3-Aminoazepan-1-yl)-1,3-dimethyl-7-(2-methylbenzyl)-3,7-dihydropurine-2,6-dione.

8-(3-Amino-azepan-1-yl)-7-(2-chloro-benzyl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione,

(R) 2-[8-(3-Amino-piperidin-1-yl)-7-(2-chloro-benzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-pyridin-2-yl-acetamide

(R) 2-[8-(3-Amino-piperidin-1-yl)-7-(2-chloro-benzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-cyclohexyl-acetamide

(R) 8-(3-Amino-piperidin-1-yl)-7-(2-chloro-benzyl)-3-methyl-1-(2-oxo-2-pyrrolidin-1-yl-ethyl)-3,7-dihydro-purine-2,6-dione

(R) 2-[8-(3-Aminopiperidin-1-yl)-7-(2-chlorobenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-cyclopentylacetamide.

2-[8-(3-(R) Amino-piperidin-1-yl)-7-(2-chloro-benzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-N-(1-aza-bicyclo[2.2.2]oct-3-yl)-acetamide

(R) 2-[8-(3-Amino-piperidin-1-yl)-7-(2-chloro-benzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-(3-hydroxy-pyridin-2-yl)-acetamide

(R,R) 8-(3-Amino-piperidin-1-yl)-7-(2-chloro-benzyl)-1-[2-(3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-3-methyl-3,7-dihydro-purine-2,6-dione

(R) 2-[8-(3-Amino-piperidin-1-yl)-7-benzyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-pyridin-2-yl-acetamide

(R) 2-[8-(3-Amino-piperidin-1-yl)-7-benzyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-cyclohexyl-acetamide

(R) 2-[8-(3-Amino-piperidin-1-yl)-7-benzyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-cyclopentyl-acetamide

2-[8-(3-(R)-Amino-piperidin-1-yl)-7-benzyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-(1-aza-bicyclo[2.2.2]oct-3-yl)-acetamide

(R) 2-[8-(3-Amino-piperidin-1-yl)-7-benzyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-(3-hydroxy-pyridin-2-yl)-acetamide

(R) 2-[8-(3-Amino-piperidin-1-yl)-7-benzyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-pyridin-3-yl-acetamide

(R) 2-[8-(3-Amino-piperidin-1-yl)-7-(2-cyano-benzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-(6-amino-pyridin-2-yl)-acetamide

(R) 2-[8-(3-Amino-piperidin-1-yl)-7-(2-cyano-benzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-pyridin-2-yl-acetamide

(R) 2-[8-(3-Amino-piperidin-1-yl)-7-(2-cyano-benzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-(3-hydroxy-pyridin-2-yl)-acetamide

(R) 8-(3-Amino-piperidin-1-yl)-1,3-dimethyl-7-thiophen-2-ylmethyl-3,7-dihydro-purine-2,6-dione

The compounds of the present invention may be chiral, and it is intended that any hemisuccinate salts of enantiomers, as separated, pure or partially purified enantiomers or racemic mixtures thereof are included within the scope of the invention.

Furthermore, when a double bond or a fully or partially saturated ring system or more than one centre of asymmetry or a bond with restricted rotatability is present in the molecule diastereomers may be formed. It is intended that any hemisuccinate salts of diastereomers, as separated, pure or partially purified diastereomers or mixtures thereof are included within the scope of the invention.

Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any hemisuccinate salts of tautomeric forms, which the compounds are able to form, are included within the scope of the present invention.

Hemisuccinate salts of compounds of formula I may be used for the manufacture of a medicament for treating diseases associated with proteins that are subject to inactivation by DPP-IV.

A further aspect of the invention is the use of a hemisuccinate salt of a compound of the invention for the manufacture of a medicament for treating a condition that may be regulated or normalised via inhibition of DPP-IV.

Another aspect of the invention is the use of a hemisuccinate salt of a compound of the invention for the manufacture of a medicament for treatment of metabolic disorders.

Another aspect of the invention is the use of a hemisuccinate salt of a compound of the invention for the manufacture of a medicament for blood glucose lowering.

Another aspect of the invention is the use of a hemisuccinate salt of a compound of the invention for the manufacture of a medicament for treatment of Type 2 diabetes

Another aspect of the invention is the use of a hemisuccinate salt of a compound of the invention for the manufacture of a medicament for the treatment of impaired glucose tolerance (IGT).

Another aspect of the invention is the use of a hemisuccinate salt of a compound of the invention for the manufacture of a medicament for the treatment of impaired fasting glucose (IFG).

Another aspect of the invention is the use of a hemisuccinate salt of a compound of the invention for the manufacture of a medicament for prevention of hyperglycemia.

Another aspect of the invention is the use of a hemisuccinate salt of a compound of the invention for the manufacture of a medicament for delaying the progression of impaired glucose tolerance (IGT) to Type 2 diabetes.

Another aspect of the invention is the use of a hemisuccinate salt of a compound of the invention for the manufacture of a medicament for delaying the progression of non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

Another aspect of the invention is the use of a hemisuccinate salt of a compound of the invention for the manufacture of a medicament for increasing the number and/or the size of beta cells in a mammalian subject.

Another aspect of the invention is the use of a hemisuccinate salt of a compound of the invention for the manufacture of a medicament for treatment of beta cell degeneration, in particular apoptosis of beta cells.

Another aspect of the invention is the use of a hemisuccinate salt of a compound of the invention for the manufacture of a medicament for the treatment of disorders of food intake.

Another aspect of the invention is the use of a hemisuccinate salt of a compound of the invention for the manufacture of a medicament for the treatment of obesity.

Another aspect of the invention is the use of a hemisuccinate salt of a compound of the invention for the manufacture of a medicament for appetite regulation or induction of satiety.

Another aspect of the invention is the use of a hemisuccinate salt of a compound of the invention for the manufacture of a medicament for the treatment of dyslipidemia.

Another aspect of the invention is the use of a hemisuccinate salt of a compound of the invention for the manufacture of a medicament for treatment of functional dyspepsia, in particular irritable bowel syndrome.

A further aspect of the invention is a method for treating the conditions mentioned above by administering to a subject in need thereof an effective amount of a hemisuccinate salt of a compound of the invention.

It is to be understood that the invention extends to all of the stereo isomeric forms of the claimed compounds, as well as the racemates.

PHARMACEUTICAL COMPOSITIONS

In another aspect, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one hemisuccinate salt of a

compound of the invention which inhibits the enzymatic activity of DPP-IV or a pharmaceutically acceptable salt or prodrug or hydrate thereof together with a pharmaceutically acceptable carrier or diluent.

Pharmaceutical compositions containing a hemisuccinate salt of a compound of the invention of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practise of Pharmacy, 19th Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a hemisuccinate salt of a compound of the invention which inhibits the enzymatic activity of DPP-IV or a pharmaceutically acceptable basic addition salt or prodrug or hydrate thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the hemisuccinate salt of an active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the hemisuccinate salt of an active compound. The hemisuccinate salt of an active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, cyclodextrin, amylose, magnesium stearate, talc, gelatine, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring sub-

stances and the like, which do not deleteriously react with the hemisuccinate salt of an active compounds.

The route of administration may be any route, which effectively transports the active hemisuccinate salt of a compound of the invention which inhibits the enzymatic activity of DPP-IV to the appropriate or desired site of action, such as oral, nasal, pulmonary, buccal, subdermal, intradermal, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain a hemisuccinate salt of a compound of the invention which inhibits the enzymatic activity of DPP-IV, dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the hemisuccinate salt of an active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet which may be prepared by conventional tabletting techniques may contain:

Core:	
Active compound (as hemisuccinate salt)	250 mg
Colloidal silicon dioxide (Aerosil)®	1.5 mg
Cellulose, microcryst. (Avicel)®	70 mg
Modified cellulose gum (Ac-Di-Sol)®	7.5 mg
Magnesium stearate	**Ad.**

Coating:	
HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

The hemisuccinate salts of compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, per day may be used. A most preferable dosage is about 0.5 mg to about 250 mg per day. In choosing a regimen for patients it may frequently be necessary to begin with a higher dosage and when the condition is under control to reduce the dosage. The exact dosage will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

Generally, the hemisuccinate salts of compounds of the present invention are dispensed in unit dosage form comprising from about 0.05 to about 1000 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration comprise from about 0.05 mg to about 1000 mg, preferably from about 0.5 mg to about 250 mg of the hemisuccinate salts of compounds admixed with a pharmaceutically acceptable carrier or diluent.

The invention also encompasses prodrugs of a hemisuccinate salt of a compound of the invention which on administration undergo chemical conversion by metabolic processes before becoming active pharmacological substances. In general, such prodrugs will be functional derivatives of hemisuccinate salts of a compound of the invention which are readily convertible in vivo into a compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Combination treatments

The invention furthermore relates to the use of hemisuccinate salts of a compound according to the present invention for the preparation of a medicament for use in the treatment of diabetes in a regimen which additionally comprises treatment with another antidiabetic agent.

In the present context the expression "antidiabetic agent" includes compounds for the treatment and/or prophylaxis of insulin resistance and diseases wherein insulin resistance is the pathophysiological mechanism.

In one embodiment of this invention, the antidiabetic agent is insulin or GLP-1 or any analogue or derivative thereof.

In another embodiment the antidiabetic agent is a hypoglycaemic agent, preferably an oral hypoglycaemic agent.

Oral hypoglycaemic agents are preferably selected from the group consisting of sulfonylureas, non-sulphonylurea insulin secretagogues, biguanides, thiazolidinediones, alpha glucosidase inhibitors, glucagon antagonists, GLP-1 agonists, potasium channel openers, insulin sensitizers, hepatic enzyme inhibitors, glucose uptake modulators, compounds modifying the lipid metabolism, compounds lowering food intake, and agents acting on the ATP-dependent potassium channel of the ß-cells.

Among the sulfonylureas, tolbutamide, glibenclamide, glipizide and gliclazide are preferred.

Among the non-sulphonylurea insulin secretagogues, repaglinide and nateglinide are preferred.

Among the biguanides, metformin is preferred.

Among the thiazolidinediones, troglitazone, rosiglitazone and ciglitazone are preferred.

Among the glucosidase inhibitors, acarbose is preferred.

Among the agents acting on the ATP-dependent potassium channel of the ß-cells the following are preferred: glibenclamide, glipizide, gliclazide, repaglinide.

The cyclic amines used in the synthesis of the compounds herein are either commercially available, or have been made using published procedures. Racemic 3-aminopiperidine was made from 3-aminopyridine by reduction with PtO_2 (Nienburg. Chem. Ber. 70(1937)635). Enantiopure (R)- and (S)-3-aminopiperidine and (R)- and (S)-3-Aminopyrrolidine was made according to Moon, S-H and Lee, S. Synth. Commun. 28(1998)3919.

PHARMACOLOGICAL METHODS

Methods for measuring the activity of compounds which inhibit the enzymatic activity of CD26/DPP-IV

Summary.

Chemical compounds are tested for their ability to inhibit the enzyme activity of purified CD26/DPP-IV. Briefly, the activity of CD26/DPP-IV is measured *in vitro* by its ability to cleave the synthetic substrate Gly-Pro-p-nitroanilide (Gly-Pro-pNA). Cleavage of Gly-Pro-pNA by DPP-IV liberates the product p-nitroanilide (pNA), whose rate of appearance is directly proportional to the enzyme activity. Inhibition of the enzyme activity by specific enzyme inhibitors slows down the generation of pNA. Stronger interaction between an inhibitor and the enzyme results in a slower rate of generation of pNA. Thus, the degree of inhibition of the rate of accumulation of pNA is a direct measure of the strength of enzyme inhibition. The accumulation of pNA is measured spectrophotometrically. The inhibition constant, Ki, for each compound is determined by incubating fixed amounts of enzyme with several different concentrations of inhibitor and substrate.

Materials:

The following reagents and cells are commercially available:

Porcine CD26/DPP-IV (Sigma D-7052), Gly-Pro-pNA (Sigma G0513).

Assay buffer: 50 mM Tris pH 7.4, 150 mM NaCl, 0,1% Triton X-100.

Gly-Pro-pNA cleavage-assay for CD26:

The activity of purified CD26/DPP-IV is assayed in reactions containing:

70 µl assay buffer

10 µl inhibitor or buffer

10 µl substrate (Gly-Pro-pNA from a 0.1M stock solution in water) or buffer

10 µl enzyme or buffer

Reactions containing identical amounts of enzyme, but varying concentrations of inhibitor and substrate, or buffer as control, are set up in parallel in individual wells of a 96-well ELISA plate. The plate is incubated at 25 °C and absorbance is read at 405 nm after 60 min incubation. The inhibitor constants are calculated by non-linear regression hyperbolic fit and the result is expressed as inhibition constant (Ki) in nM.

Diabetes model

The Zucker Diabetic Fatty (ZDF) rat model can be used to investigate the effects of the hemisuccinate salt of compounds of the invention on both the treatment and prevention of diabetes as rats of this sub-strain are initially pre-diabetic although develop severe type 2 diabetes characterised by increased HbA1c levels over a period of 6 weeks. The same strain can be used to predict the clinical efficacy of other anti-diabetic drug types. For example, the model predicts the potency and limited clinical efficacy of thiazolidinedione insulin sensitizers compounds.

EXAMPLES

Preparative HPLC (Method A1)

Column: 1.9 x 15 cm Waters XTerra RP-18. Buffer: linear gradient 5 – 95% in 15 min, MeCN, 0.1% TFA, flow rate of 15 ml/min. The pooled fractions are either evaporated to dryness *in vacuo*, or evaporated *in vacuo* until the MeCN is removed, and then frozen and freeze dried.

Preparative HPLC (Method A2) D9.1.19

Column: Supelcosil ABZ+Plus, 25 cm x 10 mm, 5 µm. Solvent A: 0.1% TFA/Water, solvent B: MeCN. Eluent composition: 5 min. 100% A, linear gradient 0 – 100% B in 7 min, 100% B in 2 min. Flow rate 5 ml/min. The column is allowed to equilibrate for 4 min in 100% A before the next run.

Preparative HPLC (Method A3) HDemPrep

The LC system consists of a Gilson 321 pump, 235 injector and 215-fraction collector equipped with a Waters Xterra 7.8 mm * 100 mm column run with a gradient from 10 % aqueous acetonitril with 0.01% TFA to 100 % acetonitril with 0.01% TFA over 11 min. Flow rate 10 ml/min. The effluent is split 1:1000 to an Agilent 1100 MSD by a LC Packings ACM 10-50 flow splitter. The MS is equipped with an Agilent fraction collector kit, from which the analogue signal from extracted the target ion, is used for controlling fraction collection.

HPLC-MS (Method B) (Anyone)

Column: Waters Xterra MS C-18 X 3 mm id. Buffer: Linear gradient 10 - 100% in 7.5 min, MeCN, 0.01% TFA, flow rate 1.0 ml/min. Detection 210 nm (analog output from

diode array detector), MS-detection ionisation mode API-ES, scan 100-1000 amu step 0.1 amu.

HPLC-MS (Method C) (h8)

Column: 0.3 mm x 15 cm Waters Symmetry C_{18}. Buffer: Linear gradient 5 - 90% in 15 min, MeCN, 0.05% TFA, flow rate 1 ml/min

Analytical separation of stereoisomers (Method D)

CCE, Chiral capillary electrophoresis: Conditions: HP 3D Capillary Electrophoresis: 48.5/40cm, 50µm HP bubble capillary, Electrolyte: HS-β-CD (Regis) (2% w/v) in 50mM phosphate buffer pH2.5 (HP), Voltage: -17kV, Injection: 30mbar for 5s.

Preparative separation of stereoisomers (Method E)

Analytical separations were performed on Hewlett Packard 1090 HPLC equipment with 5 chiral Daicel columns (AD, OD, AS, OJ and Welko-O2, 250 x 4.6 mm) with a diode array detector. The mobile phases were 2-propanol:heptane mixtures with 0.1% DEA.

Preparative separations were performed with the above-mentioned type of columns (250 x 20 mm) on a preparative Gilson HPLC set-up. Relevant fractions were collected and evaporated (SpeedVac).

Microwave assisted reactions (Method F)

The reactants are mixed in an appropriate solvent in a closed teflon vessel (XP 1500 Plus Vessel set) and heated in a micro wave oven (CEM MARSX microwave instrument. Magnetron frequency: 2455 MHz. Power Output: 1200 Watt.). The reaction mixture is cooled and evaporated *in vacuo*. Normally solvents like MeOH, EtOH, iPrOH, H2O, DMF and DMSO are used.

Chiral capillary electrophoresis (CCE) analysis of 3-aminopiperidine (Method G)

The chiral analysis of 3-aminopiperidine consists of a derivatisation step prior to chiral analysis using capillary electrophoresis (CE).

Derivatisation, 50µl 40mM 3-aminopiperidine solution in water is added to 200µl 40mM OPA solution (40mM OPA in 1:15:185 mercaptaethanol:MeOH:water). The reaction in carried out in the dark within 2 minutes. 50µl of this reaction mixture is diluted with 950µl water and analysed directly on the CE instrument.

CE instrumentation and conditions, HP^{3D}CE instrument equipped with a 48.5/40.0cm bubble cell capillary and detection at 226nm UV. The injection was 50mbar in 4.0 seconds.. The applied voltage was +19kV which yielded +60µA and prior to each injection the capillary was washed with 0.1N NaOH for 1 minute and electrolyte for 1.5 minutes. The electrolyte was 0.5% (w/v) carboxyethyl-β-cyclodextrin (Cyclolab, Hungary) dissolved in 50mM fosphate buffer pH 7.0. The two enantiomers migrate within 5 minutes of electrophoresis and the identity of specific enantiomers is confirmed by spiking of the racemate.

Preparation of (R) piperidine-3-ylamine

Step A: (R) N-CBz nipecotic acid

R (-) Ethylnipeconate tartaric acid salt (117 g, 382 mmol) was dissolved in 2N NaOH (1200 ml, 2.40 mol) and cooled to 5 °C. Z-OSu (100 g, 401 mmol) dissolved in 100 ml THF was added to the chilled reaction. The mixture was allowed to stir at 5 °C for 1 h. and at RT overnight. Approx. 100 ml of solvent was removed by rotary evaporation *in vacuo*, and the remaining solution was acidified to pH 2 – 3 with conc. HCl (app. 75 ml). The resulting crystal were isolated by filtration and dried *in vacuo* overnight.

Yield 86 g (85 %)

^{1}H-NMR (dmso-d6, 400 MHz) δ: 12.5 (s broad, 1H), (7.42 – 7.30 (m, 5H), 5.1 (s, 2H), 4.0 (s, 1H), 3.80 (s, 1H), 3.12 (m, 1H), 2.92 (t, 1H), 2.36 (m, 1H), 1.92 (m, 1H), 1.7 – 1.48 (m, 2H), 1.48 – 1.30 (m, 1H). HPLC-MS (Method B): *m/z* = 264 (M+1), R_t = 3.30 min.

Step B: (R) 3-tert-Butoxycarbonylamino-piperidine-1-carboxylic acid benzyl ester

(R) N-CBz nipecotic acid (86 g, 327 mmol) was dissolved in toluene (100 ml) and evaporated to dryness three times. tert. Butanol (1000 ml, 10.5 mmol) and triethylamine (50.1 ml, 359 mmol) were added to the reaction mixture. The reaction mixture was stirred for 30 min., and DPPA (98.5 ml, 457 mmol) was added over 15 min. The reaction mixture was heated to 100 °C overnight. After cooling, the solvent was removed by evaporation *in vacuo*, and water (200 ml) was added. After overnight stirring at RT the product was isolated by fil-

tration, and stirred with EtOAc (250 ml) for one hour. The EtOAc solution was filtered and evaporated *in vacuo* to give the crude product as a white solid. This material was dissolved in hot EtOAc (200 ml), and cooled to 5 °C overnight. The precipitated product was isolated by filtration, washed with cold EtOAc and dried.

Yield 50.0 g (46 %).

^{1}H-NMR (dmso-d6, 400 MHz) δ: 7.32 (s, 5H), 5.12 (s, 2H), 4.6 (s, 1H), 3.8 – 3.15 (m, 5H), 1.85 (m, 1H), 1.65 (s, 1H),1.6 – 1.35 (m, 11H).

Step C: (R) Piperidin-3-yl-carbamic acid tert.-butyl ester

(R) 3-tert-Butoxycarbonylamino-piperidine-1-carboxylic acid benzyl ester (50 g, 150 mmol) was dissolved in abs. EtOH (500 ml), and hydrogenated (1 atm, 7 days, 10 % Pd/C (5.0 g)) at RT. The reaction was filtered and evaporated in vacuo to give the product as a white solid .

Yield 27.3 g (92 %).

^{1}H-NMR (dmso-d6, 300 MHz) δ: 6.85 (d, 1H), 3.41 (s br, 2H), 3.05 (m, 1H), 2.90 (m, 1H), 2.58 – 2.35 (m, 2H), 1.92 (m, 1H), 1.75 (m, 1H), 1.58 (s, 9H), 1.50 – 1.40 (m, 2H).

For analysis a small sample of the product (50 mg) was dissolved in EtOAc (2 ml), treated with 3 N HCl in EtOAc (2 ml), and evaporated in vacuo. The product was stirred with EtOAc (5 ml) for one hour and filtered to give (R) 3-aminopiperidine in > 98 % ee, (determined as described in method G).

Preparation of Azepan-3-ylamine

3-Amino-azepan-2-one (24,0g, 0,188mol) was dissolved in THF and cooled on an ice bath in a nitrogen atmosphere. $LiAlH_4$ (35,6g, 0.938 mol) was added in small portions. After the last addition the re-action mixture was allowed to warm up to room temperature and stirred for 72 hours, then refluxed for 48 hours. Water was added very slowly until a white reaction mixture was obtained. K_2CO_3 was added until a filterable slurry was obtained. Then the reaction mixture was filtered, and the precipitate was washed with THF (3 x 300 ml). The combined THF phase was evaporated in vacuo giving the title compound as a yellow oil. No further purification was performed.

HPLC-MS: (Method B): m/z = 115 (M+1), R t= 0.53 min, Purity (UV) = 99%.

^{1}H-NMR (MeOD-d_4): δ: 4.5 (s, 3H), 2.8-3.0 (m, 4H), 2.45-2.6 (m, 1H), 1.9 (m, 1H), 1.4-1.75 (m, 5H).

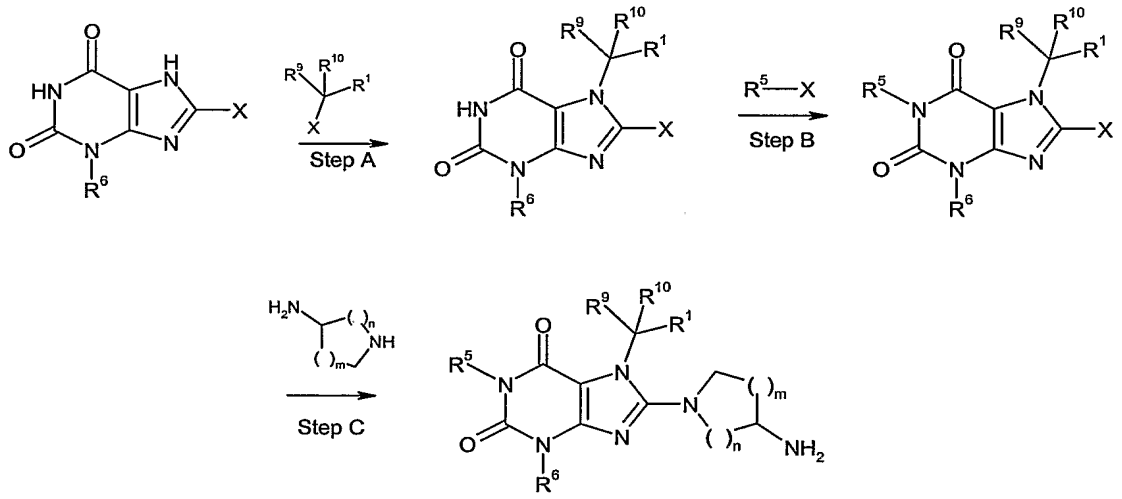
^{13}C-NMR (MeOD-d_4): δ: 57.68, 54.40, 50.19, 38.04, 31.79, 24.01.

Abbreviations

CBz	Carbobenzoxycarbonyl
EtOAc	Ethyl acetate
DCM	Dichloromethane
DEA	Diethylamine
DIEA	Diisopropylethylamine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DPPA	Diphenylphosphonic azide
HOAc	Acetic acid
MeCN	Acetonitrile
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMG	Tetramethylguanidine

The following general procedures are used to synthesize compounds of formula I. These are subsequently converted to hemisuccinate salts using the methods described below

General procedure (A):



Step A:

The starting material (16 µmol) is dissolved in a mixture of DMF and DIEA (3% DIEA, 250 µl). The alkylation reagent R^1-CR^9R^9-X (16.8 µmol, 1.05 equiv) is dissolved in DMF (100 µl) and added. The mixture is heated to 65 °C for 2h.

Step B:

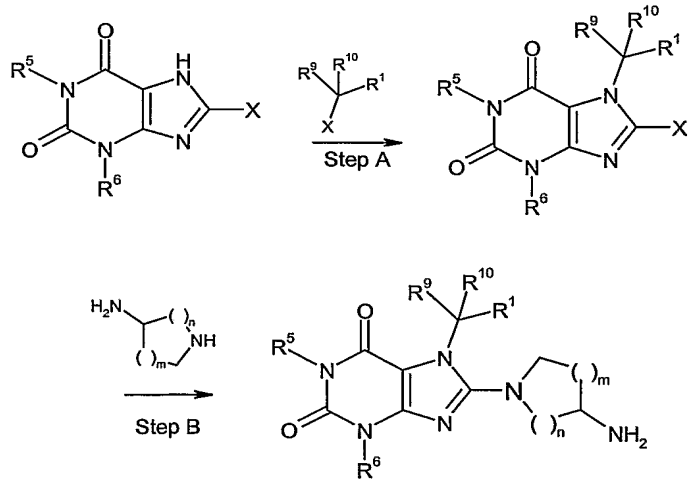
Alkylation reagent R^5-Br (32 µmol) is dissolved in DMF (100 µl) and added to the reaction mixture followed by a solution of TMG in DMF (1.16 ml TMG diluted to 5.8 ml, 48 µl). The mixture is kept at 65 °C for 4h.

Step C:

The diamine (200 µmol) is dissolved in a mixture of DMF and DIEA (3% DIEA, 200 µl) and added to the reaction mixture. The reaction is kept at 50 °C for 24h.

Samples are neutralized using HOAc (20 µl), stripped and purified by HPLC. Samples are dissolved in DMSO/H_2O (4:1, 500 µl).

General procedure (B)



Step A:

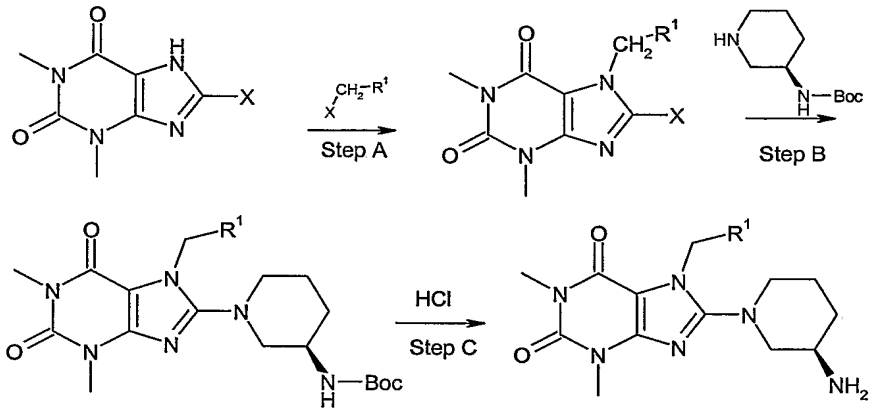
The starting material (16 µmol) is dissolved in a mixture of DMF and DIEA (3% DIEA, 250 µl). The alkylation reagent R^1-CR^9R^9-X (16.8 µmol, 1.05 equiv) is dissolved in DMF (100 µl) and added. The mixture is heated to 65°C for 2h.

Step B:

Diamine (200 µmol) is dissolved in a mixture of DMF and DIEA (3% DIEA, 200 µl) and added to the reaction mixture. The reaction is kept at 50°C for 24-48h, and then all volatiles are stripped.

Samples are neutralized using HOAc (20 µl), stripped and purified by HPLC methods A1, A2 or A3. Samples are dissolved in DMSO/H_2O (4:1, 500 µl).

General procedure C



Step A:

8-Chlorotheophylline (1 eq.) and K_2CO_3 (2.2 eq) is slurried in DMF (app. 12 ml/g of 8-Chlorotheophylline). The benzyl chloride (or bromide) is added (1.1 eq), and the slurry is stirred until the reaction is finished (1 – 7 days) at RT. The reaction mixture is poured into water (app. 70 ml/g 8-Chlorotheophylline) and stirred until the precipitation of the product has completed.

The product is filtered and dried *in vacuo*.

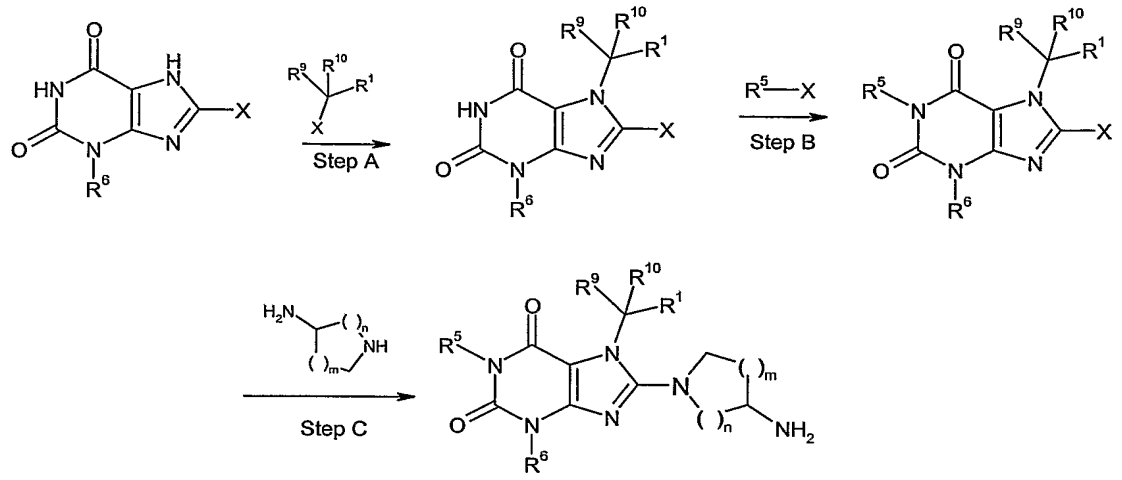
Step B:

The benzylated 8-Chlorotheophylline (1 eq.) is dissolved in DMSO (app. 35 ml/g), K_2CO_3 (4 eq.) is added, and then (R) Piperidin-3-yl-carbamic acid tert.-butyl ester (2 eq.) is added, and the reaction is stirred at either RT, 50 °C, or at 65 °C until finished (usually overnight). The reaction mixture is poured into water (4 – 10 ml / ml DMSO) with stirring, and the precipitated product is isolated by filtration, and washed with water, and dried.

Step C:

The product from step B (1 eq.) is dissolved in MeCN (app. 20 ml / g), and conc. HCl is added (10 eq.). The reaction is left with stirring overnight, and evaporated *in vacuo*. The product is dissolved in EtOAc and water (1 + 1, app. 50 ml/g), separated, and the aqueous phase washed with EtOAc (2 x 25 ml/g). The aqueous phase is added an equal amount of 2N K_2CO_3, and extracted with EtOAc (3 x 25 ml/g). The combined EtOAc phase is washed with brine, dried ($MgSO_4$), and about half the solvent is removed by evaporation in vacuo. Conc. HCl is added (1.1 eq.), and the solvent is evaporated *in vacuo*. The product is dissolved in hot EtOH, precipitated with Et_2O, collected by filtration, and dried *in vacuo*.

General procedure (D):



Step A:

The starting material (32 µmol) is dissolved in a mixture of DMF and DIEA (3% DIEA, 500 µl). The alkylation reagent R^1-CR^9R^9-X (33.6 µmol, 1.05 equiv) is dissolved in DMF (200 µl) and added. The mixture is heated to 65 °C for 2h. Upon cooling to 25 °C, K_2CO_3 (aq) is added (5.12M, 50 µL, 256 umol). Volatiles are stripped.

Step B:

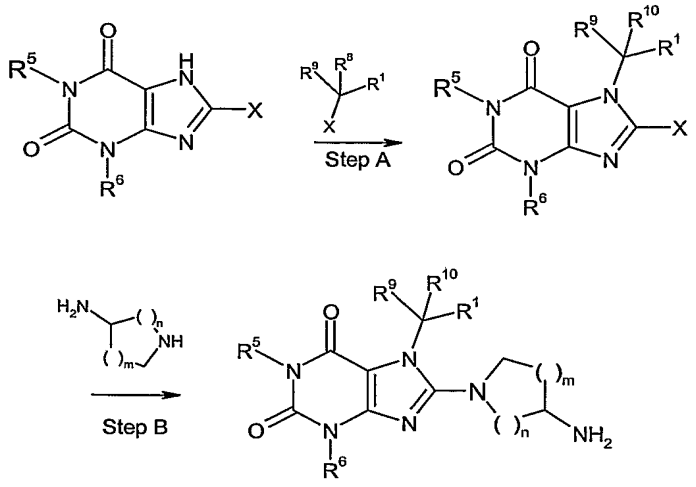
Alkylation reagent R^5-Br (64 µmol) is dissolved in DMF (250 µl) and added to the reaction mixture. The mixture is kept at 25 °C for 48h. Volatiles are stripped

Step C:

The diamine (400 µmol) is dissolved in DMSO and added to the reaction mixture. If the dihydrochloride salt of the diamine is employed, four equivalents of DCHMA is added. The reaction is kept at 50 °C for 48h.

Samples are neutralized using HOAc (30 µl), and purified by HPLC Method A3

General procedure (E):



Step A:

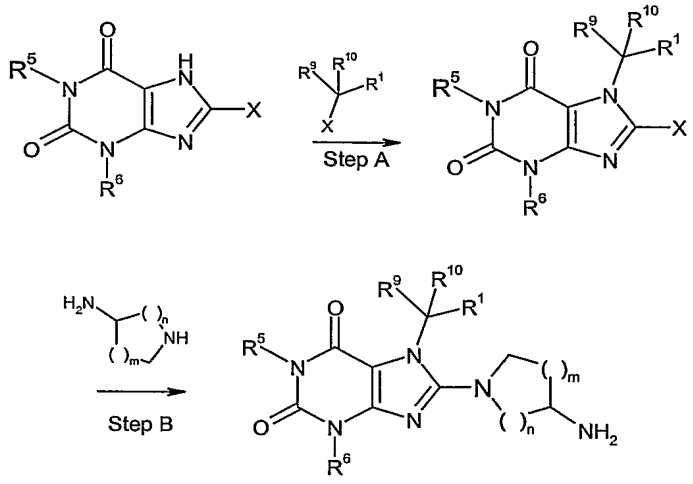
The starting material (4.08 mmol) is dissolved in a mixture of DMF and DIEA (3% DIEA, 65 ml). The alkylation reagent R^1-CR^9R^9-X (4.28 mmol, 1.05 equiv) is dissolved in DMF (25.5 ml) and added. The mixture is heated to 65°C for 2h and poured onto ice followed by filtration of the alkylated product.

Step B:

Diamine (400 µmol) is dissolved in DMSO (400 µl) and added to the above product (32 umol). The reaction is kept at 50°C for 24-48h.

Samples are neutralized using HOAc (30 µl) and purified by HPLC Method A1 or HPLC Method A2

General procedure (F):



Step A:

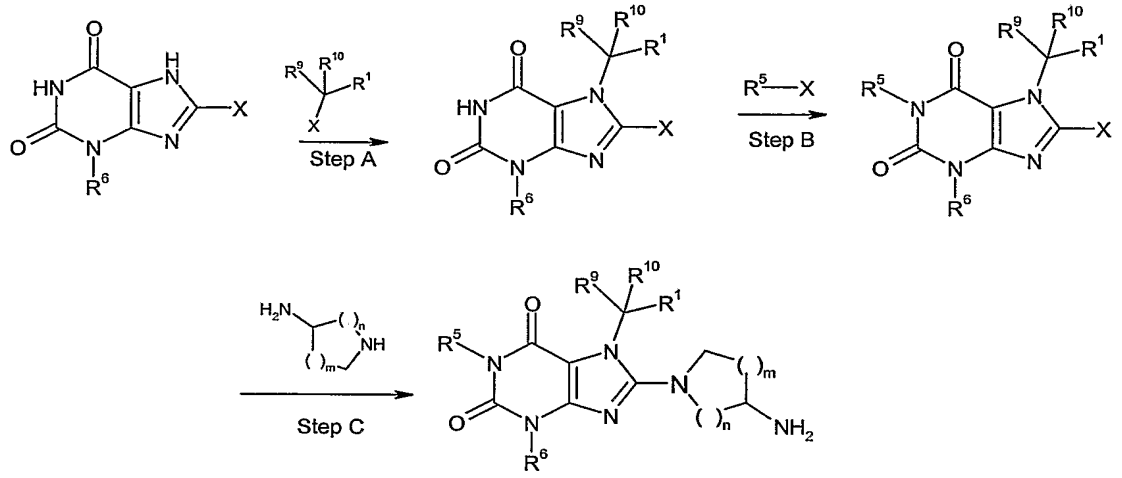
The starting material (32 µmol) is dissolved in a mixture of DMF and DIEA (3% DIEA, 500 µl). The alkylation reagent R^1-CR^9R^9-X (33.6 µmol, 1.05 equiv) is dissolved in DMF (200 µl) and added. The mixture is heated to 65°C for 2h.

Step B:

Diamine (400 µmol) is dissolved in DMSO (400 µl) and added to the above reaction mixture. The reaction is kept at 50°C for 48h.

Samples are neutralized using HOAc (30 µl) and purified by HPLC Method A2 or A3.

General procedure (G):



Step A:

The starting material (20.40 mmol) is dissolved in DMF (50 ml) and DIEA (10 ml). The alkylation reagent R^1-CR^9R^9-X (22.03 mmol, 1.08 equiv) is dissolved in DMF (10 ml) and added. Heating the mixture to 65 °C for 2h affords the products that are isolated by filtration upon adding the reaction mixture onto ice (300 ml).

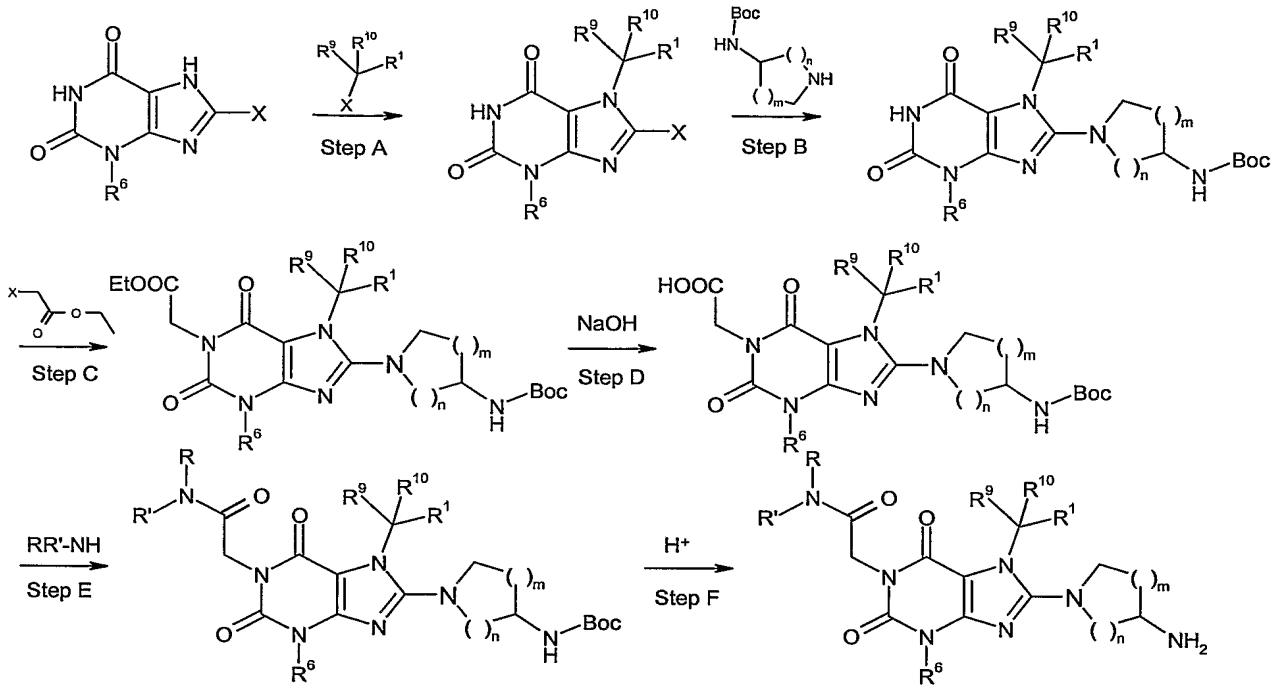
Step B:

The product from Step A (5.56 mmol) and alkylation reagent R^5-Br (11.11 mmol) are dissolved in DMF (60 ml) and potassium carbonate is added to the reaction mixture. Upon stirring at 25 °C for 16h the reaction mixture is poured onto ice (300 ml) and the product is isolated by filtration and dried *in vacuo*.

Step C:

The product from Step B (0.472 mmol) is dissolved in DMSO (5 ml) and the diamine (2.36 mmol) is added to the reaction mixture. If the dihydrochloride salt of the diamine is employed, K_2CO_3 (2.36 mmol) is added. The reaction is kept at 50 °C for 24h and poured onto ice (20 ml). The product is isolated by filtration. The compounds may be purified by HPLC methods A1, A2 or A3 or by treatment with hot acetonitrile.

General procedure (H):



Step A:

The starting material (20.40 mmol) is dissolved in DMF (50 ml) and DIEA (10 ml). The alkylation reagent R^1-CR^9R^9-X (22.03 mmol, 1.08 equiv) is dissolved in DMF (10 ml) and added. Heating the mixture to 65 °C for 2h affords the products that are isolated by filtration upon adding the reaction mixture onto ice (300 ml).

Step B:

The product from step A is dissolved in DMSO (app. 40 ml/g), DIEA (2 eq.) is added, and then (R) Piperidin-3-yl-carbamic acid tert.-butyl ester (2 eq.) is added, and the reaction is stirred at either RT, 50 °C, or at 65 °C until finished (usually overnight). The reaction mixture is poured into ice/water (4 – 10 ml / ml DMSO) with stirring, and the precipitated product is isolated by filtration, and washed with water, and dried.

Step C:

The product from step B is dissolved in DMF (1 eq. app. 10 ml/g). Ethyl 2-bromoacetate is added (2 eq.) is added, K_2CO_3 (3.5 eq) is further added, and the reaction is left with stirring at RT until completed. The reaction is poured onto ice/water (app. 100 ml), and the precipitated product is isolated by filtration, and washed with water, and dried.

Step D:

The product from step C is dissolved in EtOH (25 ml) with stirring, added 1 N NaOH (6 ml), and left with stirring overnight. HOAc (6 ml) is added, and the solvent is evaporated. The residue is poured onto ice/water (app. 100 ml), and the precipitated product is isolated by filtration, and washed with water, and dried.

Step E:

The product from step D (1 eq. 20 µmol) is dissolved in a solution of Carbonyldiimidazole (1.5 eq. 30 µM) in DMF (250 µl), and left for 2 hours. The amine NRR' (2 eq. 40 µM), dissolved in DMF (50 µl), was added and the reaction left with stirring overnight at RT. Another portion of the amine was added as before, and the reaction left with stirring overnight. The product was isolated by evaporation of the solvent.

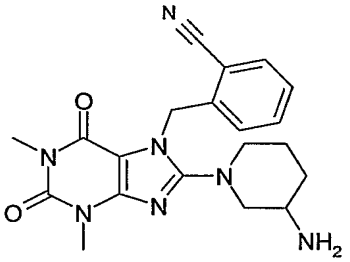
Step F:

The product from step E was added TFA in DCM (200 µl 1:1), and the reaction was left for 2 hours. Evaporation of the solvent overnight gave the product, which may be further purified by prep. HPLC methods A1, A2 or A3.

The following compounds are examples of compounds of Formula I that are subsequently converted to hemisuccinate salts.

NNC 0072-0000-1085 **Example 1**

2-(8-(3-Aminopiperidin-1-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl)benzonitrile. TFA (**1**)



NNC 0072-0000-5060-Step A: 2-(8-Chloro-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl)benzonitrile (1A)

8-Chlorotheophylline (20 g, 93.19 mmol) was dissolved in 800 ml of DMF and 2-cyanobenzyl bromide (18.28 g, 93.19 mmol), potassium carbonate (12.88 g, 93.19 mmol),

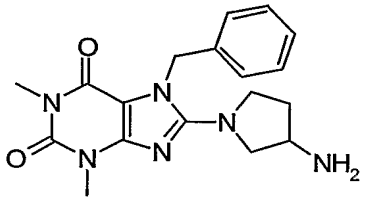
and potassium iodide (10 mg, 0.06 mmol) were added. The mixture was stirred at room temperature for 20 hours. The solvent was evaporated and the residue was suspended in 900 ml of water and 900 ml of EtOAc, and compound (1A) was collected by filtration of the suspension. The layers in the mother liquor were separated and the aqueous layer was extracted with 3 x 500 ml of EtOAc. The combined organic layers were washed with 1 x 500 ml of water, and the solvent was evaporated to give compound (1A) as white crystals.
Combined yield: 28.6 g (93 %). Mp. 222.5 - 223.7°C.
^{1}H-NMR (DMSO, 300 MHz) δ: 3.20 (s, 3H), 3.43 (s, 3H), 5.74 (s, 2H), 7.06 (d, 1H), 7.53 (t, 1H), 7.67 (t, 1H), 7.93 (d, 1H). HPLC-MS (Method B): *m/z* = 330 (M+1), R_t = 2.93 min.

NNC 0072-0000-1085-Step B: 2-(8-(3-Aminopiperidin-1-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl)benzonitrile. TFA (1)

2-(8-Chloro-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl)benzonitrile (1A) (100 mg, 0.30 mmol) and 3-aminopiperidine dihydrochloride (262 mg, 1.52 mmol) were dissolved in 20 ml of 2-propanol and triethylamine (0.127 ml, 0.91 mmol) and subjected to microwaves (method F, 130°C, 300W) for ten hours. The solvents were evaporated and the crude product was purified by preparative HPLC, (method A1, Rt = 6.78 min.) to give the title compound as oily crystals.
Yield: 66 mg (43%).
^{1}H-NMR (MeOD, 300 MHz) δ: 1.73 (m, 3H), 2.10 (m, 1H), 3.02 (m, 1H), 3.20 (m, 2H), 3.27 (s, 3H), 3.52 (m, 4H), 3.65 (m, 1H), 5.59 (s, 2H), 7.22 (d, 1H), 7.47 (m, 1H), 7.61 (m, 1H), 7.78 (d, 1H). HPLC-MS (Method B): *m/z* = 394 (M+1), R_t = 1.55 min.

Example 2

8-(3-Aminopyrrolidin-1-yl)-7-benzyl-1,3-dimethyl-3,7-dihydropurine-2,6-dione. HCl (2)



Step A: 7-Benzyl-8-chloro-1,3-dimethyl-3,7-dihydropurine-2,6-dione (2A)

8-Chlorotheophylline (50 g, 0.23 mol) was suspended in 600 ml of DMF and benzyl bromide (31 ml, 0.26 mol) and potassium carbonate (64 g, 0.46 mol) were added. The mix-

ture was stirred at room temperature for 20 hours. The solvent was evaporated and the residue was dissolved in 250 ml of water and 400 ml of DCM. The layers were separated and the aqueous layer was extracted with 150 ml of DCM. The combined organic layer was washed with 100 ml of brine, dried over magnesium sulphate, filtered, and the solvent was evaporated to give compound (2A) as white crystals.

Yield: 73.6 g (104%). Mp. 152 - 154°C.

^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.42 (s, 3H), 3.55 (s, 3H), 5.55 (s, 2H), 7.35 (m, 5H). HPLC-MS (Method B): *m/z* = 305 (M+1), R_t = 3.33 min.

Step B: 8-(3-Aminopyrrolidin-1-yl)-7-benzyl-1,3-dimethyl-3,7-dihydropurine-2,6-dione. HCl (2)

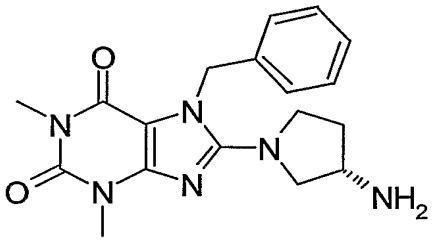
7-Benzyl-8-chloro-1,3-dimethyl-3,7-dihydropurine-2,6-dione (2A) (100 mg, 0.33 mmol) and 3-aminopyrrolidine (0.16 ml, 1.64 mmol) were dissolved in 20 ml of 2-propanol and subjected to microwaves (method F, 150°C, 300W) for one hour. The solvent was evaporated and the crude product was purified by preparative HPLC (method A1, Rt = 6.45 min.). Evaporation of the solvent afforded the title compound as a brown oil.

Yield: 111 mg (87%).

^{1}H-NMR (MeOD, 400 MHz) δ: 2.04 (m, 1H), 2.37 (m, 1H), 3.30 (s, 3H), 3.51 (s, 3H), 3.60 - 3.80 (m, 3H), 3.87 - 3.95 (m, 2H), 5.54 (d, 1H), 5.64 (d, 1H), 7.14 (d, 2H), 7.23 - 7.35 (m, 3H) HPLC-MS (Method B): *m/z* = 355 (M+1), R_t = 1.49 min.

Example 3

(S) 8-(3-Aminopyrrolidin-1-yl)-7-benzyl-1,3-dimethyl-3,7-dihydropurine-2,6-dione. HCl (3)



Step A: (S) (1-(7-Benzyl-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-8-yl)pyrrolidin-3-yl)carbamic acid tert-butyl ester (3A)

7-Benzyl-8-chloro-1,3-dimethyl-3,7-dihydropurine-2,6-dione (2A) (100 mg, 0.33 mmol), (3S)-(-)-3-(tert-butoxycarbonylamino)pyrrolidine (305 mg, 1.64 mmol), and triethylamine (0.46 ml, 3.28 mmol) was dissolved in 20 ml of 2-propanol and 5 ml of DMF and the

mixture was subjected to microwaves (method F, 130°C, 300W) for three hours. The solvent was evaporated and the crude product was purified by preparative HPLC (method A1, Rt = 11.75 min.). Evaporation of the solvent afforded compound (3A) as a brown oil.
Yield: 130 mg (87%)

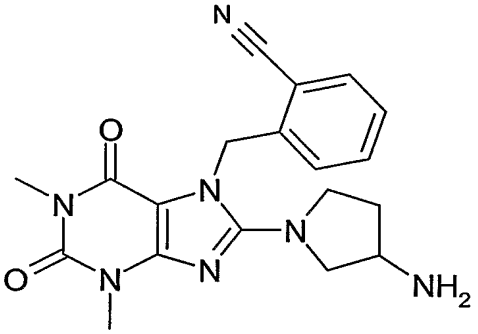
^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.42 (s, 9H), 1.89 (m, 1H), 2.12 (m, 1H), 3.34 (s, 3H), 3.37 - 3.79 (m, 7H), 4.22 (br. s, 1H), 4.97 (d, 1H), 5.49 (d, 1H), 5.55 (d, 1H), 7.04 (m, 2H), 7.28 (m, 3H). HPLC-MS (Method B): *m/z* = 455 (M+1), R_t = 3.95 min.

Step B: (S) 8-(3-Aminopyrrolidin-1-yl)-7-benzyl-1,3-dimethyl-3,7-dihydropurine-2,6-dione. HCl (3)

(S) (1-(7-Benzyl-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-8-yl)pyrrolidin-3-yl)carbamic acid tert-butyl ester (3A) (130 mg, 0.29 mmol) was dissolved in 15 ml of diethyl ether, hydrochloric acid in diethyl ether (2.5 M, 5.72 ml, 14.3 mmol) was added, and the mixture was stirred at room temperature for 24 hours. The solvents were evaporated and the crude product was suspended in dry DCM and collected by filtration to afford the title compound as white crystals.
Yield: 101 mg, (91%) Mp. 166 - 169°C.
^{1}H-NMR (MeOD, 300 MHz) δ: 2.05 (m, 1H), 2.37 (m, 1H), 3.29 (s, 3H), 3.52 (s, 3H), 3.58 - 3.97 (m, 5H), 5.53 (d, 1H), 5.63 (d, 1H), 7.13 (d, 2H), 7.21 - 7.36 (m, 3H).
HPLC-MS (Method B): *m/z* = 355 (M+1), R_t = 1.52 min.

Example 4

2-(8-(3-Aminopyrrolidin-1-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl)benzonitrile. HCl (4)



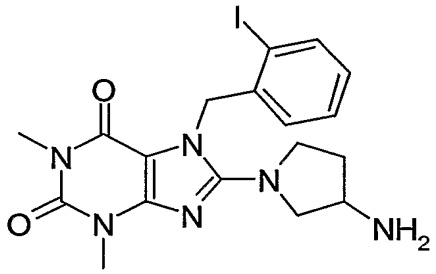
2-(8-Chloro-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl)benzonitrile (1A) (100 mg, 0.30 mmol) and 3-aminopyrrolidine (0.15 ml, 1.52 mmol) were reacted and purified as described in example **2**, step B, to give the title compound as a yellow foam.
Yield: 108 mg (76%). Mp.186 - 189°C.

Prep. HPLC (method A1): R_t = 6.19 min.

^{1}H-NMR (MeOD, 400 MHz) δ: 2.09 (m, 1H), 2.40 (m, 1H), 3.27 (s, 3H), 3.50 (s, 3H), 3.59 - 3.78 (m, 3H), 3.88 - 3.99 (m, 2H), 5.70 (d, 1H), 5.79 (d, 1H), 7.12 (d, 1H), 7.49 (dd, 1H), 7.62 (dd, 1H), 7.80 (d, 1H). HPLC-MS (Method B): *m/z* = 380 (M+1), R_t = 1.35 min.

Example 5

8-(3-Aminopyrrolidin-1-yl)-7-(2-iodobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione. HCl (**5**)



NNC 0072-0000-5069-Step A: 8-Chloro-7-(2-iodobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione (5A)

8-Chlorotheophylline (8.5 g, 39.6 mmol) was dissolved in 400 ml of DMF and 2-iodobenzyl chloride (10.0 g, 39.6 mmol), potassium carbonate (5.47 g, 39.6 mmol), and potassium iodide (10 mg, 0.06 mmol) were added. The mixture was stirred at room temperature for 7 days. Water (2500 ml) and EtOAc (800 ml) were added and the layers were separated. The aqueous layer was extracted with 2 x 500 ml of EtOAc, and the combined organic layer was washed with 500 ml of water, 500 ml of brine, dried over sodium sulphate, and filtered. The solvent was evaporated and the crude product was crystallized from diethyl ether and petrol, to give compound (5A) as white crystals. The mother liquor was evaporated and resuspended in diethyl ether and petrol, to give a second crop of compound (5A).
Combined yield: 10.4 g (61%). Mp. 177.6 - 178.2°C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.37 (s, 3H), 3.61 (s, 3H), 5.59 (s, 2H), 6.48 (d, 1H), 7.02 (t, 1H), 7.27 (t, 1H), 7.90 (d, 1H). HPLC-MS (Method B): *m/z* = 431 (M+1), R_t = 3.94 min.

Step B: 8-(3-Aminopyrrolidin-1-yl)-7-(2-iodobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione. HCl (5)

8-Chloro-7-(2-iodobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione (5A) (100 mg, 0.23 mmol) and 3-aminopyrrolidine (0.13 ml, 1.16 mmol) were reacted and purified as described in example 2, step B, to give the crude product, which was further suspended in dry DCM, and filtered to afford the title compound as white crystals.

Yield: 77 mg (64%).

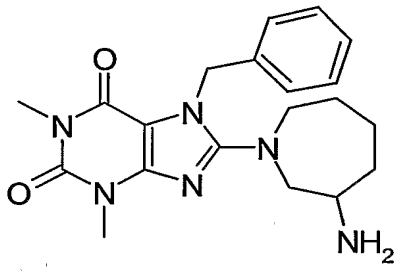
Prep. HPLC (method A1): R_t = 7.28 min.

^{1}H-NMR (MeOD, 200 MHz) δ: 2.02 (m, 1H), 2.35 (m, 1H), 3.27 (s, 3H), 3.47 - 3.74 (m, 6H), 3.82 - 3.93 (m, 2H), 5.44 (d, 1H), 5.53 (d, 1H), 6.72 (d, 1H), 7.04 (dd, 1H), 7.32 (dd, 1H), 7.92 (d, 1H). HPLC-MS (Method B): *m/z* = 481 (M+1), R_t = 1.76 min.

Preparative separation of compound (5) (Method E) gave compound (7) (Rt: 20,0 min, 95,9 % ee) and compound (15) (Rt: 16,5 min, 95.5 % ee).

Example 6

8-(3-Aminoazepan-1-yl)-7-benzyl-1,3-dimethyl-3,7-dihydropurine-2,6-dione. TFA (6)



Step A: N-(2-Oxoazepan-3-yl)-4-methylbenzenesulfonamide (6A)

DL-3-Amino-E-caprolactam (3 g, 23.4 mmol) was dissolved in 140 ml of dry DCM and dry triethylamine (4.5 ml) and 4-toluenesulfonyl chloride (4.5 g, 23.6 mmol) were added. The reaction was stirred for 3 days at room temperature and then filtered through celite. The filtrate was extracted with 50 ml of 1M aqueous potassium hydrogen sulphate, 50 ml of saturated sodium hydrogen carbonate, 50 ml of water, and 50 ml of brine, and dried over sodium sulphate. The solvent was evaporated and the residue suspended in dry dichloromethane, and compound (6A) was collected by filtration. The mother liquor was evaporated and resuspended in DCM, to give a second crop of compound (6A) as white crystals.

Combined yield: 5.99 g (90%). Mp. 179.9 - 180.5°C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.34 (m, 1H), 1.55 - 1.85 (m, 3H), 2.00 (m, 1H), 2.17 (m, 1H), 2.40 (s, 3H), 3.10 (m, 2H), 3.81 (m, 1H), 5.86 (m, 1H), 6.12 (d, 1H), 7.28 (d, 2H), 7.72 (d, 2H). HPLC-MS (Method B): *m/z* = 283 (M+1), R_t = 2.71 min.

Step B: N-(Azepan-3-yl)-4-methylbenzenesulfonamide (6B)

N-(2-Oxoazepan-3-yl)-4-methylbenzenesulfonamide (6A) (4.24 g, 15 mmol) was dissolved in 250 ml of dry THF under a nitrogen atmosphere, and lithium aluminium hydride (1.11 g, 30 mmol) was added slowly. The reaction was heated to reflux for 20 hours and then quenched with water until the effervescence ceased. Solid potassium carbonate was added until a white suspension appeared, and the mixture was allowed to stir for half an hour. The suspension was filtered through celite, which was washed with 3 x 50 ml of EtOAc. The solvents were evaporated and the residue was dissolved in 100 ml of EtOAc and 100 ml of water. The layers were separated and the aqueous layer was extracted with 2 x 100 ml of EtOAc. The combined organic layer was washed with brine, dried over sodium sulphate, and evaporated to give compound (6B) as an oil.

Yield: 2.89 g (71%).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.37 - 1.74 (m, 6H), 2.41 (s, 3H), 2.55 - 2.93 (m, 4H), 3.45 (m, 1H), 7.27 (d, 2H), 7.76 (d, 2H). HPLC-MS (Method B): *m/z* = 269 (M+1), R_t = 1.43 min.

Step C: N-(1-(7-Benzyl-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-8-yl)azepan-3-yl)-4-methylbenzenesulfonamide (6C)

7-Benzyl-8-chloro-1,3-dimethyl-3,7-dihydropurine-2,6-dione (2A) (1.03 g, 3.40 mmol) and N-(azepan-3-yl)-4-methylbenzenesulfonamide (6B) (1.00 g, 3.73 mmol) were dissolved in 2-methoxyethanol (30 ml) and triethylamine (2.4 ml), and the mixture was heated to 120°C for 2 days. The solvents were evaporated and the crude product was dissolved in 100 ml of EtOAc and 100 ml of water. The aqueous phase was acidified with 1M potassium hydrogen sulphate until pH = 2. The organic layer was separated and extracted with 50 ml of 1M aqueous potassium hydrogen sulphate, and 50 ml of brine, and dried over sodium sulphate. The solvent was evaporated and the crude product was purified by column chromatography on silica gel using EtOAc:heptane (1:1) as the eluent. Evaporation of the solvent gave compound (6C) as a white foam.

Yield: 548 mg (30%). Mp. 80.2 - 88.2°C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.22 - 1.84 (m, 6H), 2.41 (s, 3H), 3.00 (m, 1H), 3.25 (dd, 1H), 3.47 - 3.72 (m, 6H), 5.37 (d, 1H), 5.59 (d, 1H), 7.03 (d, 2H), 7.29 (m, 5H), 7.75 (d, 2H), 7.88 (d, 1H). HPLC-MS (Method B): *m/z* = 537 (M+1), R_t = 4.32 min.

Step D: 8-(3-Aminoazepan-1-yl)-7-benzyl-1,3-dimethyl-3,7-dihydropurine-2,6-dione. TFA (6)

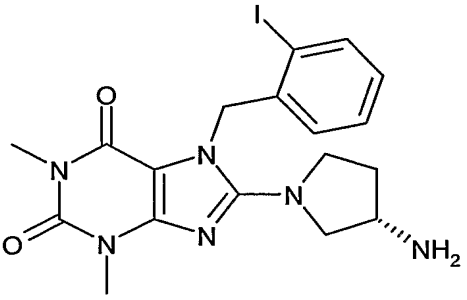
N-(1-(7-Benzyl-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-8-yl)azepan-3-yl)-4-methylbenzenesulfonamide (6C) (100 mg, 0.19 mmol) was dissolved in hydrobromic acid (48%, 5 ml) and benzene (0.07 ml), and phenol (61.4 mg, 0.65 mmol) was added. The mixture was heated to reflux for three hours, and after cooling 20 ml of EtOAc was added. The layers were separated, and the aqueous layer washed with 20 ml of EtOAc. pH was adjusted to 11 with 10M sodium hydroxide. The aqueous layer was extracted with diethyl ether (3 x 20 ml), and the combined organic layers were dried over sodium sulphate and the solvent was evaporated. The crude product was dissolved in 5 ml of DCM and 0.5 ml of trifluoroacetic acid was added. The solvents were evaporated and the crude product was purified by preparative HPLC (method A1, Rt = 7.63 min). Evaporation of the solvent gave the title compound as an oil.

Yield: 8 mg (8%).

^{1}H-NMR (DMSO, 400 MHz) δ: 1.34 (m, 1H), 1.50 (m, 2H), 1.68 (m, 2H), 1.88 (m, 1H), 3.20 (s, 3H), 3.30-3.50 (m, 5H), 3.81 (m, 1H), 5.46 (d, 1H), 5.52 (d, 1H), 7.09 (m, 2H), 7.32 (m, 3H). HPLC-MS (Method B): *m/z* = 383 (M+1), R_t = 2.00 min.

Example 7

(S) 8-(3-Aminopyrrolidin-1-yl)-7-(2-iodobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione. HCl (**7**)



Step A: (S) (1-(7-(2-Iodobenzyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-8-yl)pyrrolidin-3-yl)carbamic acid tert-butyl ester (7A)

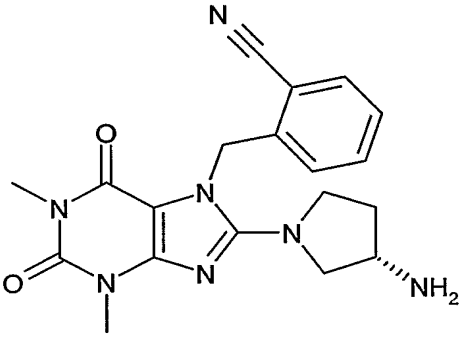
8-Chloro-7-(2-iodobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione (5A) (100 mg, 0.23 mmol) and (3S)-(-)-3-(tert-butoxycarbonylamino)pyrrolidine (216 mg, 1.16 mmol), and triethylamine (0.32 ml, 2.32 mmol) were dissolved in 20 ml of 2-propanol and the mixture was subjected to microwaves (method F, 130°C, 300W) for three hours. The solvents were evaporated and the crude product was purified by preparative HPLC (method A1, Rt = 12.99 min.). Evaporation of the solvent afforded compound (7A) as white crystals.
Yield: 132 mg (98%).
HPLC-MS (Method B): *m/z* = 581 (M+1), R_t = 4.42 min.

Step B: (S) 8-(3-Aminopyrrolidin-1-yl)-7-(2-iodobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione. HCl (7)

(S) (1-(7-(2-Iodobenzyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-8-yl)pyrrolidin-3-yl)carbamic acid tert-butyl ester (7A) (132 mg, 0.23 mmol) was reacted and purified as described in example 3, step B, to give the title compound as white crystals.
Yield: 84 mg (72%). Mp. 119 - 223°C.
^{1}H-NMR (MeOD, 300 MHz) δ: 2.03 (m, 1H), 2.34 (m, 1H), 3.26 (s, 3H), 3.52 (m, 4H), 3.65 (m, 2H), 3.90 (m, 2H), 5.45 (d, 1H), 5.52 (d, 1H), 6.73 (d, 1H), 7.04 (m, 1H), 7.32 (m, 1H), 7.92 (d, 1H). HPLC-MS (Method B): *m/z* = 481 (M+1), R_t = 1.89 min.

Example 8

(S) 2-(8-(3-Aminopyrrolidin-1-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl)benzonitrile. HCl (8)



Step A: (S) (1-(7-(2-Cyanobenzyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-8-yl)pyrrolidin-3-yl)carbamic acid tert-butyl ester (8A)

2-(8-Chloro-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl)benzonitrile (1A) (100 mg, 0.30 mmol) was reacted with (3S)-(-)-3-(tert-butoxycarbonylamino)pyrrolidine (282 mg, 1.52 mmol), and purified as described in example **7**, step A, to afford compound (8A) as white crystals.

Yield: 117 mg (81%).

Prep. HPLC, (method A1): R_t =11.50 min.

HPLC-MS (Method B): *m/z* = 480 (M+1), R_t = 3.75 min.

Step B: (S) 2-(8-(3-Aminopyrrolidin-1-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl)benzonitrile. HCl (**8**)

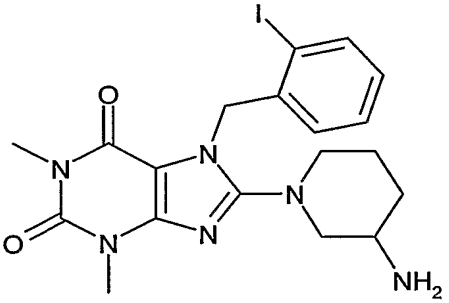
(S) (1-(7-(2-Cyanobenzyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-8-yl)pyrrolidin-3-yl)carbamic acid tert-butyl ester (8A) (117 mg, 0.24 mmol) was reacted and purified as described in example **3**, step B, to give the title compound as white crystals.

Yield: 51 mg (50%). Mp.104 - 117°C.

^{1}H-NMR (MeOD, 300 MHz) δ: 2.08 (m, 1H), 2.40 (m, 1H), 3.26 (s, 3H), 3.52 (s, 3H), 3.53 - 3.78 (m, 3H), 3.92 (m, 2H), 5.71 (d, 1H), 5.78 (d, 1H), 7.13 (d, 1H), 7.47 (m, 1H), 7.62 (m, 1H), 7.80 (d, 1H). HPLC-MS (Method B): *m/z* = 380 (M+1), R_t = 1.34 min.

Example 9

8-(3-Aminopiperidin-1-yl)-7-(2-iodobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione. TFA (**9**)



8-Chloro-7-(2-iodobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione (5A) (100 mg, 0.23 mmol) and 3-aminopiperidine dihydrochloride (202 mg, 1.16 mmol) were reacted and purified as described in example **1**, step B, to give the title compound as oily brown crystals.

Yield: 19 mg (13%).

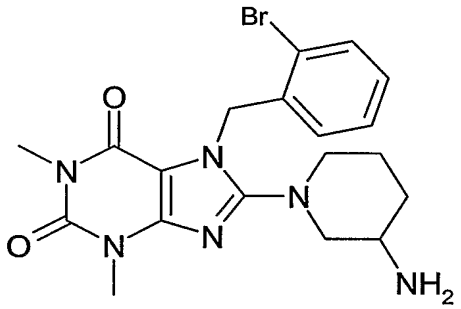
Prep. HPLC (method A1): R_t = 7.70 min.

^{1}H-NMR (MeOD, 300 MHz) δ: 1.62 (m, 2H), 1.74 (m, 1H), 2.08 (m, 1H), 2.94 (m, 1H), 3.18 (m, 2H), 3.28 (s, 3H), 3.46 (m, 1H), 3.54 (s, 3H), 3.70 (m, 1H), 5.35 (s, 2H), 6.78 (d, 1H), 7.04 (m, 1H), 7.32 (m, 1H), 7.92 (d, 1H).

HPLC-MS (Method B): *m/z* = 495 (M+1), R_t = 2.09 min.

Example 10

8-(3-Aminopiperidin-1-yl)-7-(2-bromobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione. TFA (**10**)



Step A: 7-(2-Bromobenzyl)-8-chloro-1,3-dimethyl-3,7-dihydropurine-2,6-dione (10A)

8-Chlorotheophylline (10 g, 46.6 mmol) was dissolved in 250 ml of DMF and 8 ml of DIEA, and 2-bromobenzyl bromide (12.2 g, 48.9 mmol) was added. The mixture was stirred at 65°C for 2 hours. The reaction mixture was added 20 ml of EtOAc and 250 ml of cold water. The white precipitate was collected by filtration to afford compound (10A) as white crystals.

Yield: 17.2 g (96%). Mp. 165.4 - 166.7°C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.37 (s, 3H), 3.60 (s, 3H), 5.67 (s, 2H), 6.57 (d, 1H), 7.20 (m, 2H), 7.62 (d, 1H). HPLC-MS (Method B): *m/z* = 385 (M+2), R_t = 3.77 min.

Step B: 8-(3-Aminopiperidin-1-yl)-7-(2-bromobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione. TFA (**10**)

7-(2-Bromobenzyl)-8-chloro-1,3-dimethyl-3,7-dihydropurine-2,6-dione (10A) (100 mg, 0.26 mmol) and 3-aminopiperidine dihydrochloride (226 mg, 1.31 mmol) were dissolved in 2-propanol (20 ml), triethylamine (0.109 ml, 0.78 mmol) and DMF (5 ml) and subjected to microwaves (method F, 130°C, 300W) for ten hours. The solvents were evaporated and the

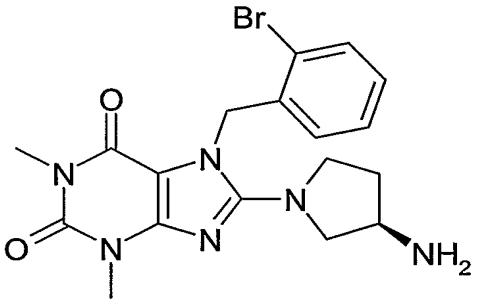
crude product was purified by preparative HPLC, (method A1, Rt = 7.52 min.) to give the title compound as a brown oil.

Yield: 10 mg (7%).

HPLC-MS (Method B): *m/z* = 447 (M+), R_t = 2.05 min.

Example 11

(R) 8-(3-Aminopyrrolidin-1-yl)-7-(2-bromobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione. TFA (**11**)



Step A: (R) (1-(7-(2-Bromobenzyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-8-yl)pyrrolidin-3-yl)carbamic acid tert-butyl ester (11A)

7-(2-Bromobenzyl)-8-chloro-1,3-dimethyl-3,7-dihydropurine-2,6-dione (10A) (100 mg, 0.26 mmol) and (3R)-(+)-3-(tert-butoxycarbonylamino)pyrrolidine (243 mg, 1.30 mmol) were reacted and purified as described in example **3**, step A, to give compound (11A) as brown crystals.

Yield: 44 mg (32%). Mp. 104 - 106°C.

Prep. HPLC, (method A1): Rt = 12.66 min.

^{1}H-NMR (MeOD, 200 MHz) δ: 1.40 (s, 9H), 1.83 (m, 1H), 2.07 (m, 1H), 3.25 (s, 3H), 3.37 (m, 1H), 3.48 - 3.78 (m, 6H), 4.04 (m, 1H), 5.57 (s, 2H), 6.74 (d, 1H), 7.23 (m, 2H), 7.62 (m, 1H).

HPLC-MS (Method B): *m/z* = 535 (M+2), R_t = 4.08 min

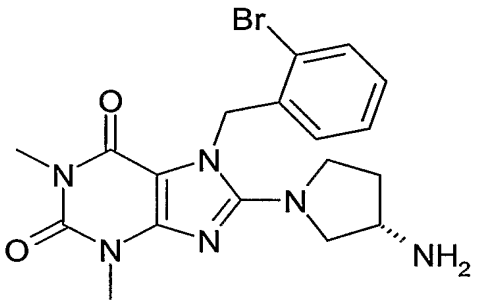
Step B: (R) 8-(3-Aminopyrrolidin-1-yl)-7-(2-bromobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione. TFA (**11**)

(R) (1-(7-(2-Bromobenzyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-8-yl)pyrrolidin-3-yl)carbamic acid tert-butyl ester (11A) (44 mg, 0.08 mmol) was dissolved in MeCN (1 ml), water (1 ml), and TFA (0.32 ml), and the mixture was stirred at room tempera-

ture for 2 days. The solvents were evaporated and the crude product was purified by preparative HPLC (method A1, Rt = 6.92 min.) to give the title compound as a brown oil.
Yield: 40 mg (88 %).
^{1}H-NMR (MeOD, 300 MHz) δ: 2.05 (m, 1H), 2.35 (m, 1H), 3.25 (s, 3H), 3.50 - 3.74 (m, 6H), 3.90 (m, 2H), 5.54 (d, 1H), 5.61 (d, 1H), 6.80 (dd, 1H), 7.21 (dt, 1H), 7.30 (dt, 1H), 7.63 (dd, 1H). HPLC-MS (Method B): *m/z* = 433 (M+), R_t = 1.83 min.

Example 12

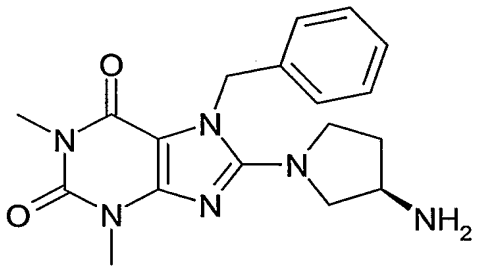
(S) 8-(3-Aminopyrrolidin-1-yl)-7-(2-bromobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione. HCl (**12**)



7-(2-Bromobenzyl)-8-chloro-1,3-dimethyl-3,7-dihydropurine-2,6-dione (10A) (100 mg, 0.26 mmol) and (S)-(-)-3-aminopyrrolidine (112 mg, 1.30 mmol) were dissolved in 2-propanol (20 ml) and DMF (5 ml) and subjected to microwaves (method F, 130°C, 300W) for 10 hours. The solvents were evaporated and the crude product was purified by preparative HPLC (method A1, Rt = 6.92 min.) to give the title compound as brown crystals.
Yield: 50 mg (41%). Mp. 215 - 217°C.
^{1}H-NMR (MeOD, 200 MHz) δ: 2.04 (m, 1H), 2.33 (m, 1H), 3.25 (s, 3H), 3.48 - 3.78 (m, 6H), 3.90 (m, 2H), 5.53 (d, 1H), 5.60 (d, 1H), 6.80 (dd, 1H), 7.25 (m, 2H), 7.63 (dd, 1H).
HPLC-MS (Method B): *m/z* = 433 (M+), R_t = 1.80 min.

Example 13

(R) 8-(3-Aminopyrrolidin-1-yl)-7-benzyl-1,3-dimethyl-3,7-dihydropurine-2,6-dione. HCl (**13**)



7-Benzyl-8-chloro-1,3-dimethyl-3,7-dihydropurine-2,6-dione (2A) (100 mg, 0.33 mmol) and (R)-(+)-3-aminopyrrolidine (141 mg, 1.64 mmol) were reacted and purified as described in example **12** to give the title compound as brown crystals.

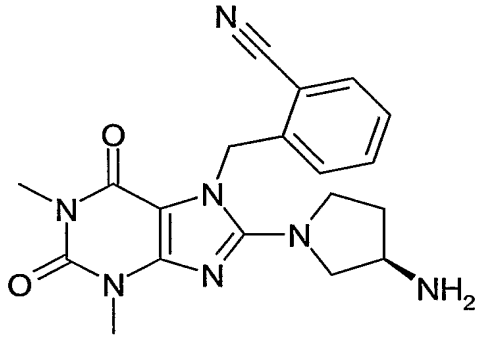
Yield: 73 mg (57%). Mp. 103 - 114°C.

Prep. HPLC, (method A1): Rt = 6.38 min.

^{1}H-NMR (MeOD, 200 MHz) δ: 2.08 (m, 1H), 2.35 (m, 1H), 3.27 (s, 3H), 3.49 (s, 3H), 3.55 - 4.00 (m, 5H), 5.52 (d, 1H), 5.63 (d, 1H), 7.12 (m, 2H), 7.29 (m, 3H). HPLC-MS (Method B): *m/z* = 355 (M+1), R_t = 1.55 min.

Example 14

(R) 2-(8-(3-Aminopyrrolidin-1-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl)benzonitrile. HCl (**14**)



2-(8-Chloro-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl)benzonitrile (1A) (100 mg, 0.30 mmol) and (R)-(+)-3-aminopyrrolidine (131 mg, 1.57 mmol) were reacted and purified as described in example **2**, step B, to give the title compound as brown crystals.

Yield: 125 mg (99%). Mp. 202 - 204°C.

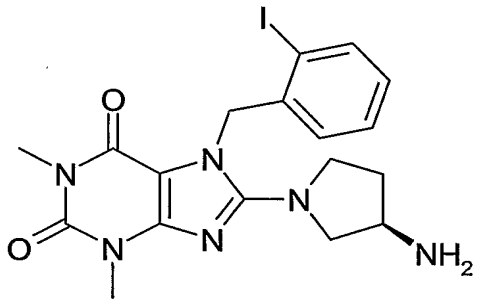
Prep. HPLC, (method A1): Rt = 6.17 min.

^{1}H-NMR (MeOD, 200 MHz) δ: 2.12 (m, 1H), 2.41 (m, 1H), 3.22 (s, 3H), 3.49 (s, 3H), 3.55 - 4.04 (m, 5H), 5.70 (d, 1H), 5.78 (d, 1H), 7.11 (d, 1H), 7.47 (t, 1H), 7.61 (t, 1H), 7.78 (d, 1H).

HPLC-MS (Method B): *m/z* = 380 (M+1), R_t = 1.38 min.

Example 15

(R) 8-(3-Aminopyrrolidin-1-yl)-7-(2-iodobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione. HCl (**15**)



8-Chloro-7-(2-iodobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione (5A) (100 mg, 0.23 mmol) and (R)-(+)-3-aminopyrrolidine (100 mg, 1.16 mmol) were reacted and purified as described in example **2**, step B, to give the title compound as white crystals.

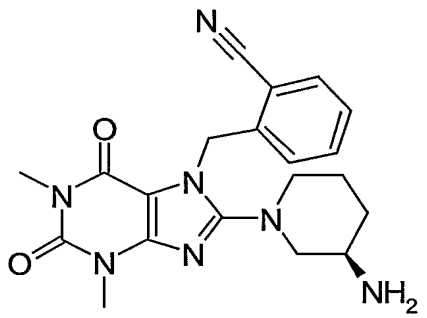
Yield: 61 mg (51%). Mp. 233 - 235°C.

Prep. HPLC, (method A1): Rt = 7.24 min.

^{1}H-NMR (MeOD, 200 MHz) δ: 2.05 (m, 1H), 2.34 (m, 1H), 3.25 (s, 3H), 3.46 - 3.76 (m, 6H), 3.90 (m, 2H), 5.43 (d, 1H), 5.52 (d, 1H), 6.72 (dd, 1H), 7.03 (dt, 1H), 7.32 (dt, 1H), 7.91 (dd, 1H). HPLC-MS (Method B): *m/z* = 481 (M+1), R_t = 1.88 min.

Example 16 (General procedure (E))

(R) 2-[8-(3-Aminopiperidin-1-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl]-benzonitrile. HCl (**16**)



Step A: 2-(8-Chloro-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl)benzonitrile (**16**A)

From 2-Cyanobenzyl bromide.

Yield: 28.6 g (93 %). Mp. 222.5 – 223.7 °C.

^{1}H-NMR (DMSO, 300 MHz) δ: 7.93 (d, 1H), 7.66 (t, 1H), 7.52 (t, 1H), 7.07 (d, 1H), 5.75 (s, 2H), 3.42 (s, 3H), 3.20 (s, 3H). HPLC-MS (Method B): *m/z* = 330 (M), R_t = 2.93 min.

Step B: (R) 1-[7-(2-Cyanobenzyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-8-yl]-piperidin-3-yl)carbamic acid tert-butyl ester (**16**B)

From (**16**A) (4g, 12.1 mmol)

Yield: 4.8 g (80%)

Step C: (R) 2-[8-(3-Aminopiperidin-1-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl]benzonitrile. HCL (16)

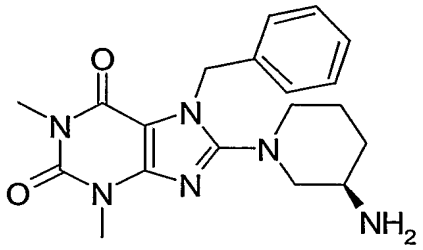
From (**16**B) (4.8 g, 9.7 mmol)

Yield: 2.49 g (59%) of the title compound.

^{1}H-NMR (CDCl3, 200 MHz) δ: 8.59(s, 2H), 7.67(m, 1H), 7.56(m, 1H), 7.39(m, 1H), 7.17(m, 1H), 5.64(s, 2H), 3.95(s, 1H), 3.68(m, 2H), 3.51(s, 4H), 3.30(s, 3H), 3.01(s, 2H), 2.00(m, 2H), 1.65(s, 1H). ^{13}C-NMR (CDCl3, 200 MHz) δ:155.76, 154.48, 151.46, 147.16, 140.17, 133.56, 133.18, 128.37, 127.47, 117.18, 110.54, 104.98, 58.07, 52.26, 51.54, 47.13, 46.91, 30.00, 27.91, 27.47, 21.72, 18.35.

Example 17 General procedure (E)

(R) 8-(3-Aminopiperidin-1-yl)-7-benzyl-1,3-dimethyl-3,7-dihydropurine-2,6-dione. HCl (**17**)



Step A: 7-Benzyl-8-chloro-1,3-dimethyl-3,7-dihydropurine-2,6-dione (**17**A)

From 8-Chlorotheophylline (50 g, 233 mmol) and benzyl bromide.

The reaction mixture was evaporated to dryness in vacuo, dissolved in DCM (400 ml) and water (250 ml). The separated aqueous phase was extracted with DCM (150 ml), and the combined DCM phases were washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*.

Yield: 73.6 g (app. 100 %). Mp. 152 - 154°C.

^{1}H-NMR (CDCl3, 200 MHz) δ: 7.35 (m, 5H), 5.55 (s, 2H), 3.55 (s, 3H), 3.42 (s, 3H).

HPLC-MS (Method B): *m/z* = 305 (M+1), R_t = 3.33 min.

Step B: (R) [1-(7-Benzyl-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-8-yl)piperidin-3-yl]carbamic acid tert-butyl ester (**17**B)

From (**17**A) (4 g, 13.1 mmol)

Yield: 5.1 g (84%)

Step C: (R) 8-(3-Aminopiperidin-1-yl)-7-benzyl-1,3-dimethyl-3,7-dihydropurine-2,6-dione. HCl (**17**)

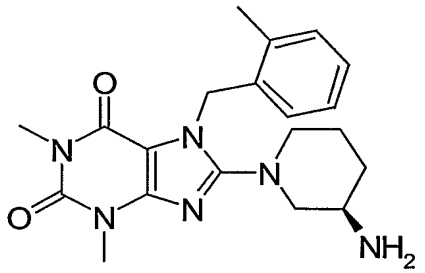
From (**17**B) (4.1 g, 10.9 mmol)

Yield: 2.6 g (67%) of the title compound.

^{1}H-NMR (CDCl3, 200 MHz) δ: 7.29(m, 5H), 5.45(dd, 2H), 3.72(m, 2H), 3.52(s, 4H), 3.37(s, 3H), 3.28(m, 1H), 3.10(m, 1H), 2.93(m, 1H), 2.14(m, 1H), 1.84(m, 2H), 1.57(s, 1H). HPLC-MS (Method B): *m/z* = 369 (M+1), R_t = 3.69 min.

Example 18 General procedure (E)

(R) 8-(3-Aminopiperidin-1-yl)-1,3-dimethyl-7-(2-methylbenzyl)-3,7-dihydropurine-2,6-dione. HCl (**18**)



Step A: 8-Chloro-1,3-dimethyl-7-(2-methylbenzyl)-3,7-dihydropurine-2,6-dione (**18**A)

From 8-Chorotheophylline (10 g, 47 mmol) and 2-methylbenzyl bromide (13.6 ml, 103 mmol). The benzyl bromide was added in two portions. First half at reaction start as described in general procedure (E), and the other half after 24 hours as the reaction had not completed.

Yield: 12.8 g (86 %). Mp.164.9 – 165.2 °C.

^{1}H-NMR (CDCl3, 200 MHz) δ: 7.3 – 7.05 (m, 3H), 6.55 (d, 1H), 5.55 (s, 2H), 3.57 (s, 3H), 3.34 (s, 3H), 2.42 (s, 3H). HPLC-MS (Method B): *m/z* = 319 (M+1), R_t = 3.76 min.

Step B: (R) (1-[1,3-Dimethyl-7-(2-methylbenzyl)-2,6-dioxo-1,2,3,6-tetrahydropurin-8-yl]piperidin-3-yl)carbamic acid tert-butyl ester (**18**B)

From (**18**A) (4 g, 12.5 mmol)

Yield: 4.9 g (82%).

Step C: (R) 8-(3-Aminopiperidin-1-yl)-1,3-dimethyl-7-(2-methylbenzyl)-3,7-dihydropurine-2,6-dione. HCl (18)

From (**18**B) (4.9 g, 10.2 mmol)

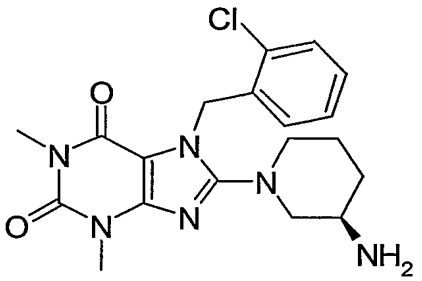
Yield: 3.27 g (76%) of the title compound.

^{1}H-NMR (CDCl3, 200 MHz) δ: 7.14(m, 3H), 6.67(d, 1H), 5.39(d, 2H), 3.80(s, 3H), 3.71(m, 1H), 3.52(s, 4H), 3.34(m, 4H), 3.02(s, 2H), 2.38(s, 3H), 2.10(s, 1H), 1.81(s, 2H), 1.54(s, 1H)

^{13}C-NMR (CDCl3, 200 MHz) δ:155.74, 154.53, 151.83, 147.29, 134.83, 134.54, 130.55, 127.61, 126.48, 124.62, 105.44, 52.03, 51.01, 46.88, 29.85, 27.92, 27.65, 22.11, 19.08.

Example 19 General procedure (E)

(R) 8-(3-Aminopiperidin-1-yl)-7-(2-chlorobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione. HCl (**19**)



Step A: 8-Chloro-7-(2-chlorobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione (**19**A)

From 8-Chorotheophylline (10 g, 47 mmol)) and 2-chlorobenzyl chloride (19.4 ml, 153.9 mmol). The 2-chlorobenzyl chloride was added in three portions. First third at reaction start as described in general procedure (E), and the other thirds after 24 and 48 hours respectively as the reaction had not completed. Total reaction time 7 days at RT. Due to incomplete precipitation in water the product was extracted with DCM (700 and 300 ml), dried ($MgSO_4$), and evaporated to dryness *in vacuo*. Excess 2-chlorobenzyl bromide was removed by washing the product in Et_2O.

Yield: 15.6 g (99 %). Mp.189.7 - 191.8 °C.

^{1}H-NMR (CDCl3, 200 MHz) δ: 7.42 (d, 1H), 7.30 – 7.12 (m, 2H, 6.67 (d, 1H), 5.7 (s, 2H), 3.57 (s, 3H), 3.35 (s, 3H). HPLC-MS (Method B): *m/z* = 339 (M+1), R_t = 3.90 min.

Step B: (R) (1-[7-(2-Chlorobenzyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-8-yl]piperidin-3-yl)carbamic acid tert-butyl ester (**19**B)

From (**19**A) (5.89 g, 17.4 mmol)

Yield: 8.87 g (app. 100%).

Step C: (R) 8-(3-Aminopiperidin-1-yl)-7-(2-chlorobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione. HCl (**19**)

From (**19**B) (8.87 g, 17.6 mmol)

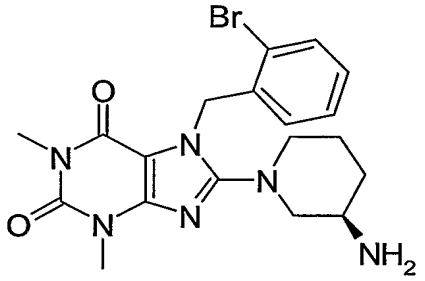
Yield: 2.49 g (59%) of the title compound.

^{1}H-NMR (CDCl3, 200 MHz) δ: 8.57(s, 3H), 7.27(m, 3H), 6.87(m, 1H), 5.47(m, 2H), 3.19 – 3.82(m, 9H), 2.97(s, 2H), 2.12(s, 1H), 1.84(m, 2H), 1.53(s, 1H)

^{13}C-NMR (CDCl3, 200 MHz) δ: 155.53, 154.34, 151.56, 147.16, 132.02, 129.64, 129.02, 127.39, 127.02, 1 05.27, 74.83, 51.93, 51.07, 46.98, 46.72, 29.93, 27.73, 22.05.

Example 20 General procedure (E)

(R) 8-(3-Aminopiperidin-1-yl)-7-(2-bromobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione. HCl (**20**)



Step A: 7-(2-Bromobenzyl)-8-chloro-1,3-dimethyl-3,7-dihydropurine-2,6-dione (**20**A)

From 8-Chorotheophylline (10 g, 46.6 mol) and 2-bromobenzyl bromide (12.2 g, 48.93 mol). Yield: 17.2 g (96%).

^{1}H-NMR (CDCl3, 200 MHz) δ: 7.62(m, 1H), 7.21(m, 2H), 6.58(m, 1H), 5.67(s, 2H), 3.60(s, 3H), 3.38(s, 3H). HPLC-MS (Method B): *m/z* = 384 (M+1).

Step B: (R) (1-[7-(2-Bromobenzyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-8-yl]piperidin-3-yl)carbamic acid tert-butyl ester (**20**B)

From (**20**A) (6.08 g, 15.8 mmol)

Yield: 8.78 g (app. 100%).

Step C: (R) 8-(3-Aminopiperidin-1-yl)-7-(2-bromobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione. HCl (**20**)

From (**20**B) (8.78 g, 16.1 mmol)

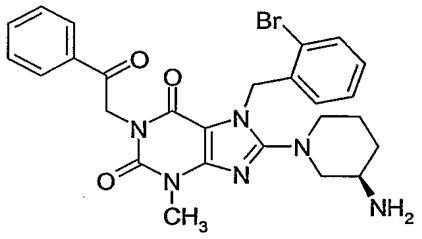
Yield: 3.73 g (52%) of the title compound.

^{1}H-NMR (MeOD, 200 MHz) δ:

^{13}C-NMR ($CDCl_3$, 200 MHz) δ:155.52, 154.28, 151.55, 147.16, 135.57, 132.92, 129.28, 128.01, 127.03, 121.78, 105.23, 51.95, 51.01, 49.19, 47.01, 29.95, 27.93, 27.81, 22.22.

Example 21 General procedure (G)

(R) 8-(3-Aminopiperidin-1-yl)-7-(2-bromobenzyl)-3-methyl-1-(2-oxo-2-phenylethyl)-3,7-dihydro-purine-2,6-dione. TFA (**21**)



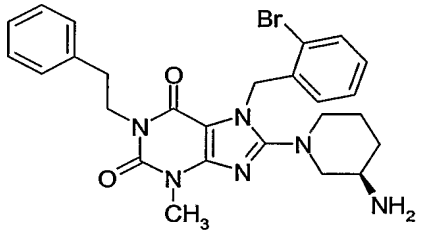
Yield: 130 mg (41%)

Prep. HPLC, (method A1): Rt = 8.86 min.

HPLC-MS (Method B): *m/z* = 551.1 (M+), R_t = 2.83 min.

Example 22 General procedure (G)

(R) 8-(3-Aminopiperidin-1-yl)-7-(2-bromobenzyl)-3-methyl-1-phenethyl-3,7-dihydropurine-2,6-dione. TFA (22)



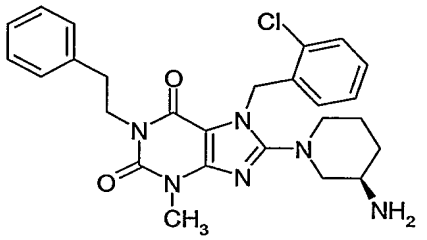
Yield: 257 mg (82%)

Prep. HPLC, (method A1): Rt = 9.20 min.

HPLC-MS (Method B): *m/z* = 539.2 (M+1), R_t = 3.23 min.

Example 23 General procedure (G)

(R) 8-(3-Aminopiperidin-1-yl)-7-(2-chlorobenzyl)-3-methyl-1-phenethyl-3,7-dihydropurine-2,6-dione. TFA (**23**)



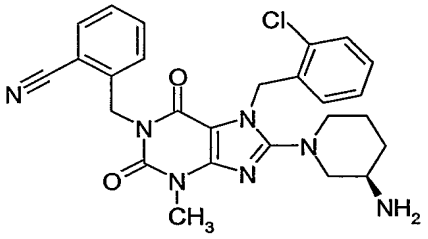
Yield: 34 mg (13%)

Prep. HPLC, (method A1): Rt = 9.83 min.

HPLC-MS (Method B): *m/z* = 493.2 (M+), R_t = 2.94 min.

Example 24 (General procedure (G))

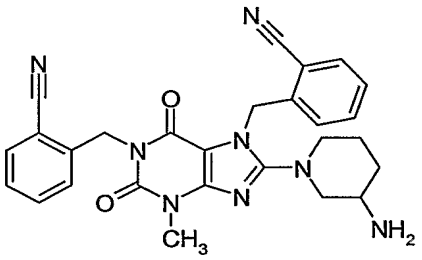
(R) 2-[8-(3-Aminopiperidin-1-yl)-7-(2-chlorobenzyl)-3-methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-1-ylmethyl]benzonitrile (**24**)



^{1}H NMR ($CDCl_3$): δ = 8.25 (s, br, 2H), 7.6 (d, 1H), 7.3 (m, 6H), 6.85 (dd, 1H), 6.3 (s, br, 1H), 5.45 (s, 1H), 5.35 (s, 2H), 5.25 (s, 1H), 3.65 (m, 3H), 3.45 (s, 3H), 3.0 (m, 2H), 2.15 - 1.3 (m,4H). HPLC-MS (Method B): *m/z* = 505 (M+1), R_t = 2.9 min.

Example 25 (General procedure (D))

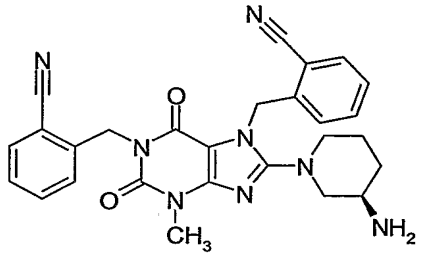
2-[8-(3-Aminopiperidin-1-yl)-7-(2-cyanobenzyl)-3-methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-1-ylmethyl]benzonitrile (**25**)



^{1}H NMR (DMSO-d_6): δ 7.87 (d, 1H), 7.80 (d, 1H), 7.65 (t, 1H), 7.57 (t, 1H), 7.49 (t, 1H), 7.42 (t, 1H), 7.12 (d, 2H), 5.54 (s, 2H), 5.15 (s, 2H), 3.42 (s, 3H), 2.86 (m, 1H), 2.64 (m, 2H), 1.78 (m, 1H), 1.66 (m, 1H), 1.47 (m, 1H), 1.15 (m, 1H). HPLC-MS (Method B): *m/z* = 495 (M+1) 518 (M+23), R_t = 2.28 min.

Example 26 (General procedure (D))

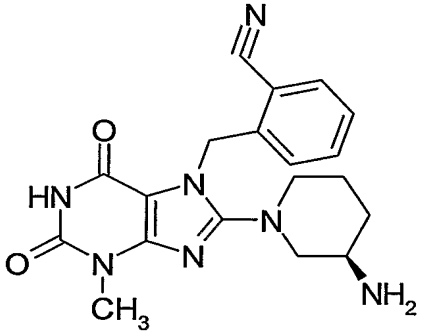
(R) 2-[8-(3-Aminopiperidin-1-yl)-7-(2-cyanobenzyl)-3-methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-1-ylmethyl]benzonitrile. TFA (**26**)



^{1}H NMR (DMSO-d_6): δ 8.1 (s, 3H), 7.87 (d, 1H), 7.80 (d, 1H), 7.70 - 7.33 (m, 4H), 7.095 (dd, 2H), 5.54 (s, 2H), 5.13 (s, 2H), 3.65- 3.53 (m, 1H), 3.43 (s, 3H), 3.40 - 3.26 (m, 1H), 3.26 - 3.05 (m, 2H), 3.01 - 2.87 (m, 1H), 2.04 - 1.68 (m, 2H), 1.65 - 1.44 (m, 2H). HPLC-MS (Method B): *m/z* = 495 (M+1), R_t = 2.503 min.

Example 27 (General procedure (E))

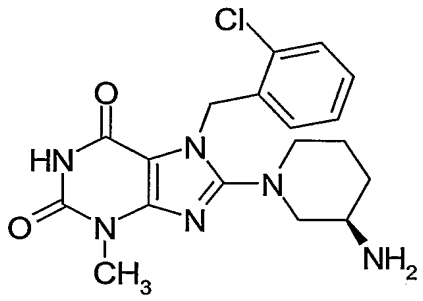
(R) 2-[8-(3-(R)-Aminopiperidin-1-yl)-3-methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl]benzonitrile. HCl (**27**)



^{1}H NMR (DMSO-d_6): δ 10.95 (s, 1H), 8.24 (s, 3H), 7.875 (d, 1H), 7.65 (t, 1H), 7.49 (t, 1H), 7.085 (d, 1H), 5.50 (s, 2H), 3.62 - 3.49 (m, 2H), 3.19 - 3.02 (m, 2H), 2.87 (t, 1H), 2.02 - 1.42 (m, 4 H). HPLC-MS (Method B): *m/z* = 380 (M+1), R_t = 1.361 min.

Example 28 (General procedure (E))

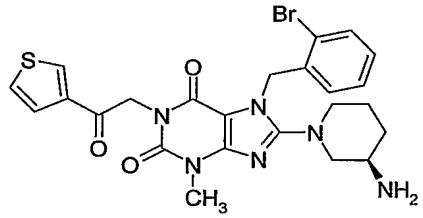
(R) 8-(3-Aminopiperidin-1-yl)-7-(2-chlorobenzyl)-3-methyl-3,7-dihydropurine-2,6-dione. HCl (**28**)



^{1}H NMR (DMSO-d_6): δ 10.95 (s, 1H), 8.35 (s br, 3H), 7.50 (d, 2H), 7.31 (dt, 2H), 6.87 (d, 1H), 5.38 (s, 2H), 3.56 (m, 1H), 3.36 (s, 3H), 3.20 (s br, 1H), 3.18-3.00 (m, 2H), 2.79 (t, 1H), 1.91 (s br, 1H), 1.72 (s br, 1H), 1.60-1.30 (m, 2H).

Example 29 (General procedure (G))

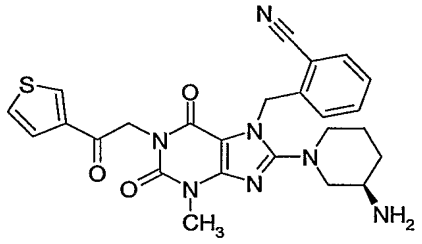
(R) 8-(3-Aminopiperidin-1-yl)-7-(2-bromobenzyl)-3-methyl-1-(2-oxo-2-thiophen-3-yl-ethyl)-3,7-dihydropurine-2,6-dione. HCl (**29**)



^{1}H NMR (DMSO-d_6): δ 8.70 (s, 1H), 8.34 (s, 3H), 7.65 -7.70(m, 2H), 7.54 (d, 1H), 7.34 (t, 1H), 7 .24 (t, 1H), 6.84 (d, 1H), 5.34 (s, 2H), 5.18 (s, 2H), 3.60-3.66 (m, 1H), 3.46 (s, 3H), 3.05-3.35(m, 3H), 2.80-2.90(m, 1H), 1.40-2.00(m, 4H). HPLC-MS (Method B): *m/z* = 558 (M+1), R_t =3.90 min.

Example 30 (General procedure (G))

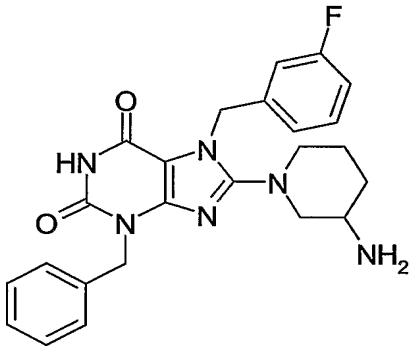
(R) 2-[8-(3-Aminopiperidin-1-yl)-3-methyl-2,6-dioxo-1-(2-oxo-2-thiophen-3-yl-ethyl)-1,2,3,6-tetrahydropurin-7-ylmethyl]benzonitrile. TFA (**30**)



^{1}H NMR (DMSO-d_6): δ 8.68-8.70 (m, 1H), 8.10-8.20 (m, 3H), 7.86 -7.90 (d, 1H), 7.45-7.70 (m, 4H), 7.05-7.10 (d, 1H), 5.53(s, 2H), 5.18 (s, 2H), 3.56-3.64 (m, 1H), 3.46 (s, 3H), 3.10-3.25(m, 2H), 2.90-3.00(m, 1H), 1.50-2.20(m, 4H). HPLC-MS (Method B): *m/z* = 504, Rt=2.23 min.

Example 31 (General procedure (F))

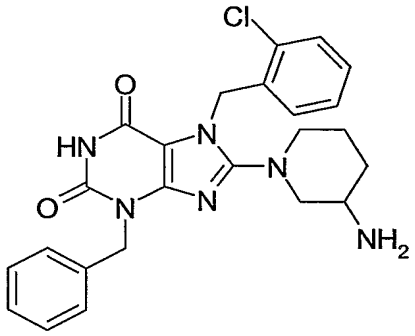
8-(3-Amino-piperidin-1-yl)-3-benzyl-7-(3-fluoro-benzyl)-3,7-dihydro-purine-2,6-dione (**31**)



HPLC-MS (Method A3): *m/z* = 449 (M+1), R_t =3.60 min.

Example 32 (General procedure (F))

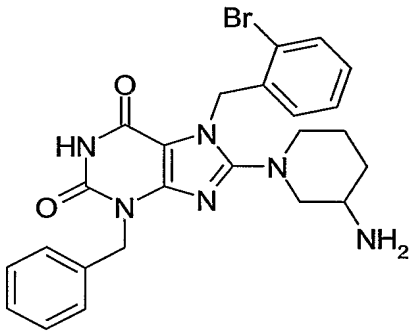
8-(3-Amino-piperidin-1-yl)-3-benzyl-7-(2-chloro-benzyl)-3,7-dihydro-purine-2,6-dione (**32**)



HPLC-MS (Method A3): *m/z* = 465 (M+1), R_t =3.40 min.

Example 33 (General procedure (F))

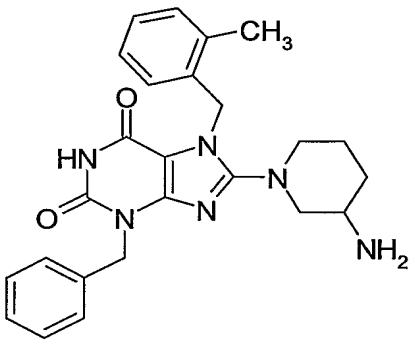
8-(3-Amino-piperidin-1-yl)-3-benzyl-7-(2-bromo-benzyl)-3,7-dihydro-purine-2,6-dione (**33**)



HPLC-MS (Method A3): *m/z* = 508 (M+1), R_t =3.50 min.

Example 34 (General procedure (F))

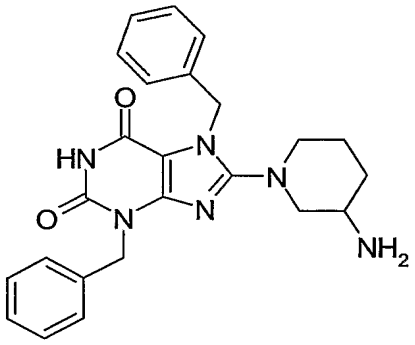
8-(3-Amino-piperidin-1-yl)-3-benzyl-7-(2-methyl-benzyl)-3,7-dihydro-purine-2,6-dione (**34**)



HPLC-MS (Method A3): *m/z* = 445 (M+1), R_t =3.50 min.

Example 35 (General procedure (F))

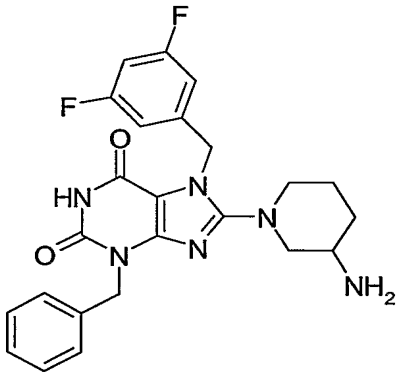
8-(3-Amino-piperidin-1-yl)-3,7-dibenzyl-3,7-dihydro-purine-2,6-dione (**35**)



HPLC-MS (Method A3): *m/z* = 431 (M+1), R_t =3.40 min.

Example 36 (General procedure (F))

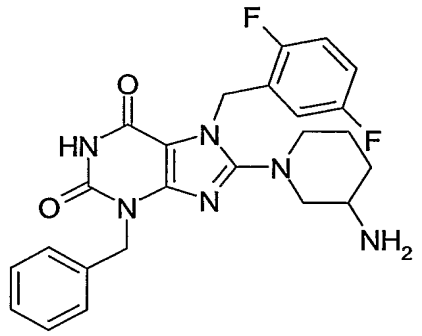
8-(3-Amino-piperidin-1-yl)-3-benzyl-7-(3,5-difluoro-benzyl)-3,7-dihydro-purine-2,6-dione (**36**)



HPLC-MS (Method A3): *m/z* = 467 (M+1), R_t =3.50 min.

Example 37 (General procedure (F))

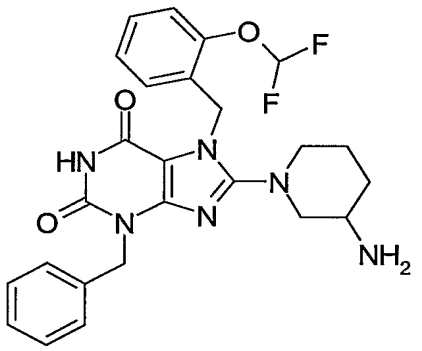
8-(3-Amino-piperidin-1-yl)-3-benzyl-7-(2,5-difluoro-benzyl)-3,7-dihydro-purine-2,6-dione (**37**)



HPLC-MS (Method A3): *m/z* = 467 (M+1), R_t =3.30 min.

Example 38 (General procedure (F))

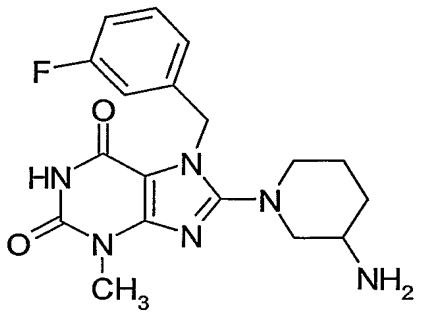
8-(3-Amino-piperidin-1-yl)-3-benzyl-7-(2-difluoromethoxy-benzyl)-3,7-dihydro-purine-2,6-dione (**38**)



HPLC-MS (Method A3): *m/z* = 497 (M+1), R_t =3.50 min.

Example 39 (General procedure (F))

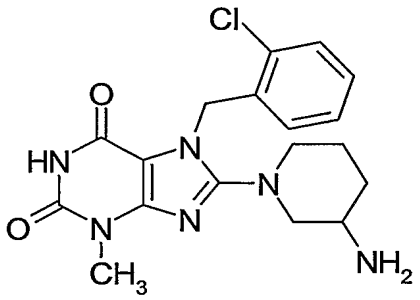
8-(3-Amino-piperidin-1-yl)-7-(3-fluoro-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione (**39**)



HPLC-MS (Method A3): *m/z* = 373 (M+1), R_t =2.30 min.

Example 40 (General procedure (F))

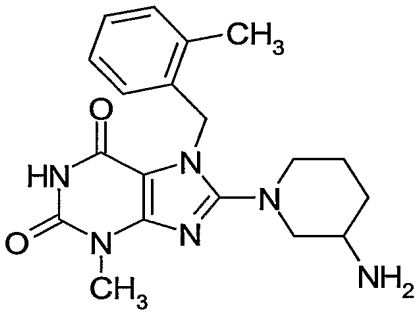
8-(3-Amino-piperidin-1-yl)-7-(2-chloro-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione (**40**)



HPLC-MS (Method A3): *m/z* = 389 (M+1), R_t =2.40 min.

Example 41 (General procedure (F))

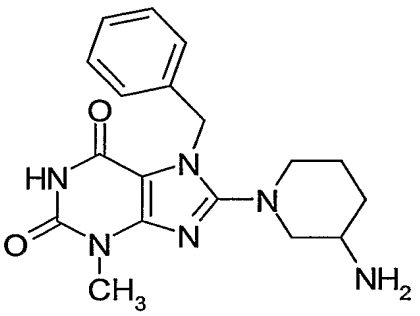
8-(3-Amino-piperidin-1-yl)-3-methyl-7-(2-methyl-benzyl)-3,7-dihydro-purine-2,6-dione (**41**)



HPLC-MS (Method A3): *m/z* = 369 (M+1), R_t =2.40 min.

Example 42 (General procedure (F))

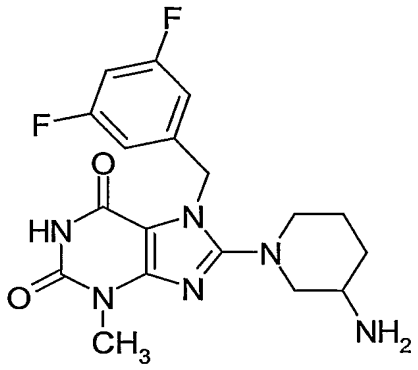
8-(3-Amino-piperidin-1-yl)-7-benzyl-3-methyl-3,7-dihydro-purine-2,6-dione (**42**)



HPLC-MS (Method A3): *m/z* = 355 (M+1), R_t =2.10 min.

Example 43 (General procedure (F))

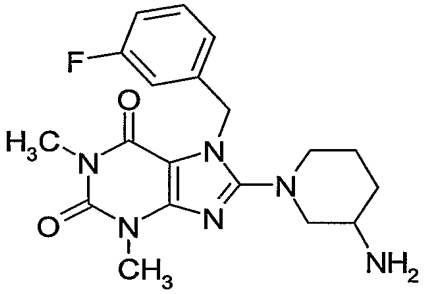
8-(3-Amino-piperidin-1-yl)-7-(3,5-difluoro-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione (**43**)



HPLC-MS (Method A3): *m/z* = 391 (M+1), R_t =2.85 min.

Example 44 (General procedure (F))

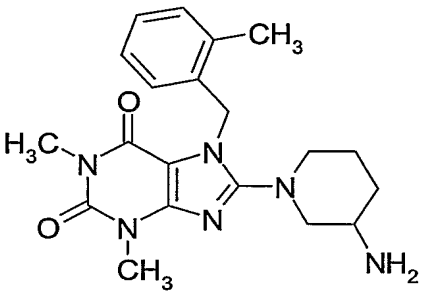
8-(3-Amino-piperidin-1-yl)-7-(3-fluoro-benzyl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione (**44**)



HPLC-MS (Method A3): *m/z* = 387 (M+1), R_t =3.10 min.

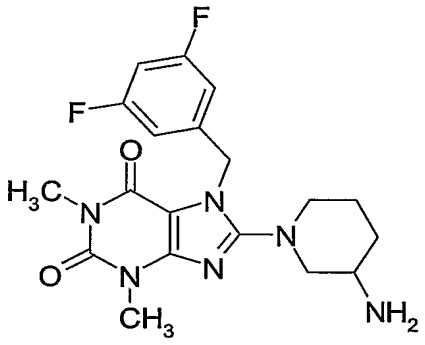
Example 45 (General procedure (F))

8-(3-Amino-piperidin-1-yl)-1,3-dimethyl-7-(2-methyl-benzyl)-3,7-dihydro-purine-2,6-dione (**45**)



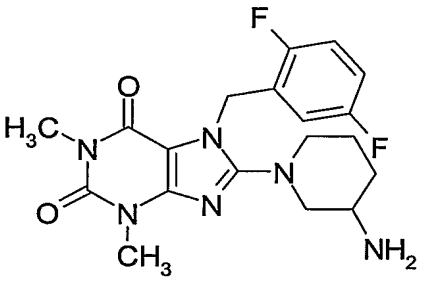
^{1}H NMR ($CDCl_3$): δ = 8.1(br. s, 3H), 7.1(m, 3H), 6.6(d, 1H), 5.4(q, 2H), 3.4-3.6(m, 6H), 3.3(s, 3H), 3.05(br. s, 2H), 1.4-2.0(m, 4H). 13C-NMR (CDCl3) δ = 155.60, 154.79, 152.01, 135,10, 134.61, 130.96, 128.06, 126.86, 124.93, 105.83, 75.09, 52.02, 51.24, 50.73, 47.10, 46.72, 30.05, 28.29, 21.12, 19.26. HPLC-MS (Method A3): *m/z* = 383 (M+1), R_t =3.20 min.

Example 46 (General procedure (F))
8-(3-Amino-piperidin-1-yl)-7-(3,5-difluoro-benzyl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione (**46**)



HPLC-MS (Method A3): *m/z* = 405 (M+1), R_t =3.10 min.

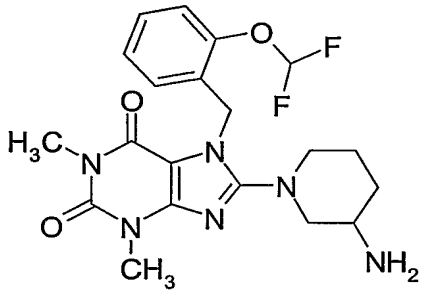
Example 47 (General procedure (F))
8-(3-Amino-piperidin-1-yl)-7-(2,5-difluoro-benzyl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione (**47**)



HPLC-MS (Method A3): *m/z* = 405 (M+1), R_t =2.80 min.

Example 48 (General procedure (F))

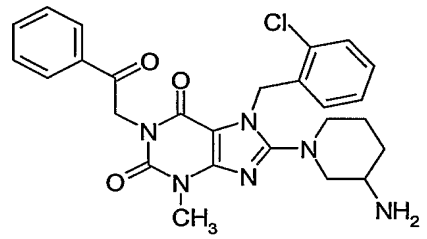
8-(3-Amino-piperidin-1-yl)-7-(2-difluoromethoxy-benzyl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione (**48**)



HPLC-MS (Method A3): *m/z* = 435 (M+1), R_t =3.10 min.

Example 49 (General procedure (A))

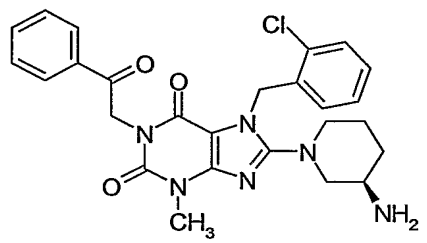
8-(3-Amino-piperidin-1-yl)-7-(2-chloro-benzyl)-3-methyl-1-(2-oxo-2-phenyl-ethyl)-3,7-dihydro-purine-2,6-dione (**49**)



^{1}H NMR (DMSO-d_6): δ 8.03 (d, 2H), 7.95 (s br, 3H), 7.70 (t, 1H), 7.56 (t, 2H), 7.49 (m, 1H), 7.31 (m, 2H), 6.88 (d, 1H), 5.39 (s, 2H), 5.30 (s, 2H), 3.63 (d, 1H), 3.25-3.15 (m, 2H), 2.05-1.20 (m, 5H). HPLC-MS (Method C): *m/z* = 507 (M+1), R_t = 4.68 min.

Example 50 (General procedure (G))

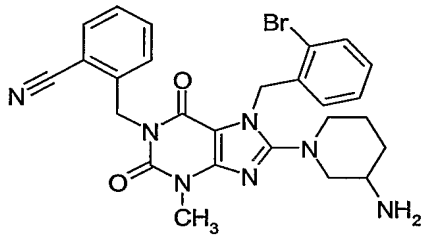
8-(R-3-Amino-piperidin-1-yl)-7-(2-chloro-benzyl)-3-methyl-1-(2-oxo-2-phenyl-ethyl)-3,7-dihydro-purine-2,6-dione (**50**)



^{1}H NMR (DMSO-d_6): δ 8.70 (s, 3H), 8.035 (d,2H), 7.70 (t, 1H), 7.57 (t, 2H), 7.53 - 7.45 (m, 1H), 7.38 - 7.25 (m, 2H), 6.93 - 6.82 (m, 1H), 5.405 (d, 2H), 5.30 (s, 2H), 6.64 (d, 1H), 3.47 (s, 3H), 3.21 - 3.06 (m, 3H), 2.94 - 2.80 (m, 1H), 2.02 - 1.34 (m, 4H). HPLC-MS (Method B): *m/z* = 507 (M+1), R_t = 2,868 min.

Example 51 (General procedure (A))

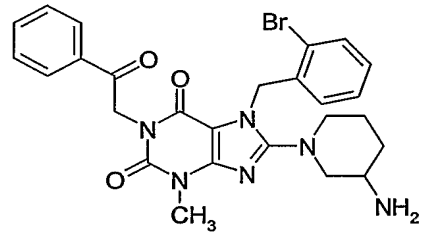
2-[8-(3-Aminopiperidin-1-yl)-7-(2-bromobenzyl)-3-methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-1-ylmethyl]benzonitrile (**51**)



^{1}H NMR (DMSO-d_6): δ 7.99 (s br, 3H), 7.80 (d, 1H), 7.67 (d, 1H), 7.58 (t, 1H), 7.42 (t, 1H), 7.34 (t, 1H), 7.25 (t, 1H), 7.16 (d, 1H), 6.87 (d, 1H), 5.34 (s, 2H), 5.15 (s, 2H), 3.62 (m, 1H), 3.40 (m, 2H), 3.45 (s, 3H), 3.20-3.05 (m, 2H), 1.95 (m, 1H), 1.80 (m, 1H), 1.55 (m, 2H). HPLC-MS (Method C): *m/z* = 548 (M+1), R_t = 4.68

Example 52 (General procedure (A))

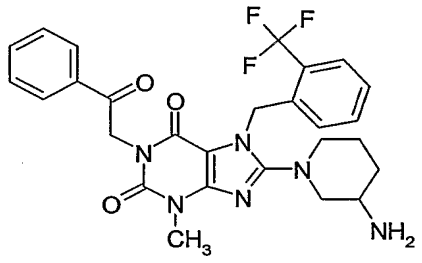
8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-3-methyl-1-(2-oxo-2-phenyl-ethyl)-3,7-dihydro-purine-2,6-dione (**52**)



^{1}H NMR (DMSO-d_6): δ 8.03 (d, 2H), 7.96 (s br, 3H), 7.72-7.65 (m, 2H), 7.56 (t, 2H), 7.35 (t, 1H), 7.25 (t, 1H), 6.83 (d, 1H), 5.34 (s, 2H), 5.30 (s, 2H), 3.62 (m, 1H), 3.47 (s, 3H), 3.20-3.05 (m, 2H), 1.95 (m, 1H), 1.80 (m, 1H), 1.55 (m, 2H). HPLC-MS (Method C): *m/z* = 551 (M+1), R_t = 4.80

Example 53 (General procedure (D))

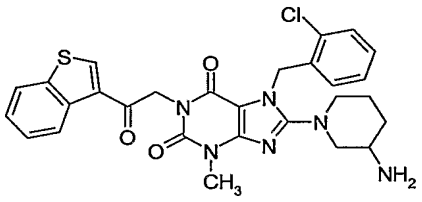
8-(3-Amino-piperidin-1-yl)-3-methyl-1-(2-oxo-2-phenyl-ethyl)-7-(2-trifluoromethyl-benzyl)-3,7-dihydro-purine-2,6-dione (**53**)



HPLC-MS (Method A3): *m/z* = 541 (M+1), R_t =4.30 min.

Example 54 (General procedure (D))

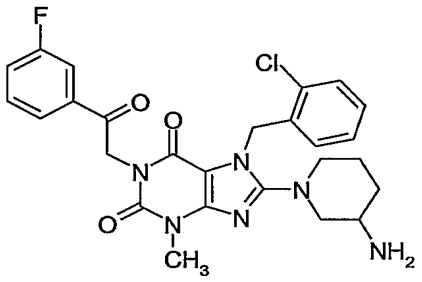
8-(3-Amino-piperidin-1-yl)-1-(2-benzo[*b*]thiophen-3-yl-2-oxo-ethyl)-7-(2-chloro-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione (**54**)



HPLC-MS (Method A3): *m/z* = 564 (M+1), R_t =4.60 min.

Example 55 (General procedure (D))

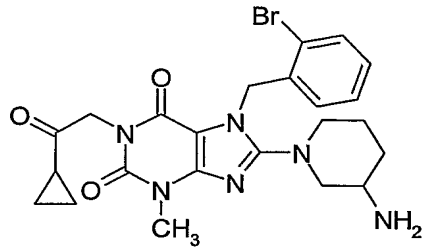
8-(3-Amino-piperidin-1-yl)-7-(2-chloro-benzyl)-1-[2-(3-fluoro-phenyl)-2-oxo-ethyl]-3-methyl-3,7-dihydro-purine-2,6-dione (**55**)



HPLC-MS (Method A3): *m/z* = 525 (M+1), R_t =4.10 min.

Example 56 (General procedure (D))

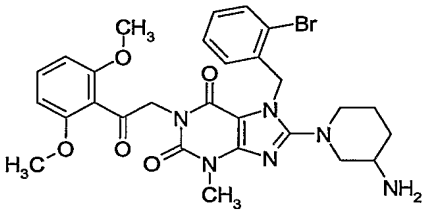
8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-1-(2-cyclopropyl-2-oxo-ethyl)-3-methyl-3,7-dihydro-purine-2,6-dione (**56**)



HPLC-MS (Method A3): *m/z* = 516 (M+1), R_t =3.40 min.

Example 57 (General procedure (D))

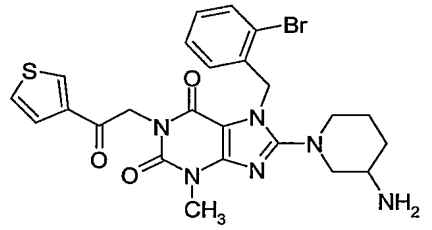
8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-1-[2-(2,6-dimethoxy-phenyl)-2-oxo-ethyl]-3-methyl-3,7-dihydro-purine-2,6-dione (**57**)



HPLC-MS (Method A3): *m/z* = 612 (M+1), R_t =4.20 min.

Example 58 (General procedure (D))

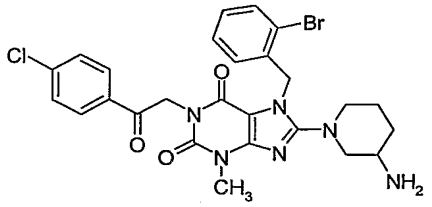
8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-3-methyl-1-(2-oxo-2-thiophen-3-yl-ethyl)-3,7-dihydro-purine-2,6-dione (**58**)



HPLC-MS (Method A3): *m/z* = 558 (M+1), R_t =3.90 min.

Example 59 (General procedure (D))

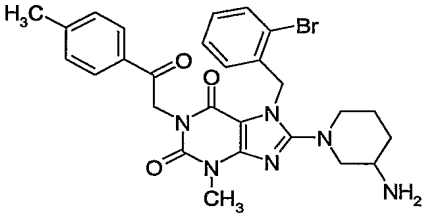
8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-1-[2-(4-chloro-phenyl)-2-oxo-ethyl]-3-methyl-3,7-dihydro-purine-2,6-dione (**59**)



HPLC-MS (Method A3): *m/z* = 586 (M+1), R_t =4.50 min.

Example 60 (General procedure (D))

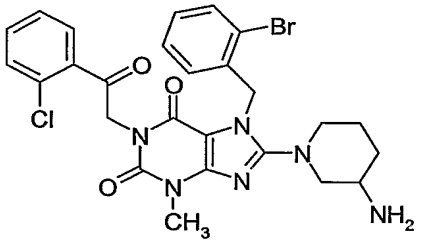
8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-3-methyl-1-(2-oxo-2-*p*-tolyl-ethyl)-3,7-dihydro-purine-2,6-dione (**60**)



HPLC-MS (Method A3): *m/z* = 566 (M+1), R_t =4.40 min.

Example 61 (General procedure (D))

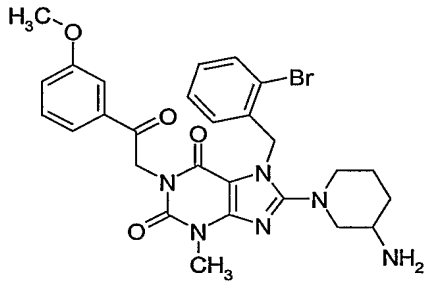
8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-1-[2-(2-chloro-phenyl)-2-oxo-ethyl]-3-methyl-3,7-dihydro-purine-2,6-dione (**61**)



HPLC-MS (Method A3): *m/z* = 586 (M+1), R_t =4.30 min.

Example 62 (General procedure (D))

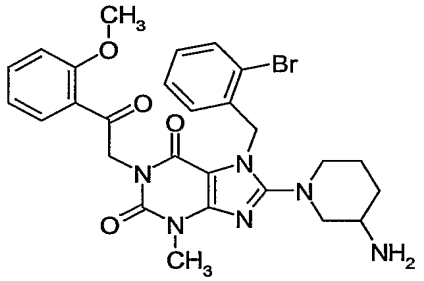
8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-1-[2-(3-methoxy-phenyl)-2-oxo-ethyl]-3-methyl-3,7-dihydro-purine-2,6-dione (**62**)



HPLC-MS (Method A3): *m/z* = 582(M+1), R_t =4.30 min.

Example 63 (General procedure (D))

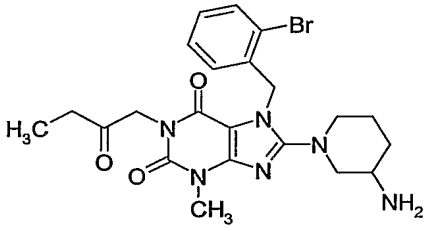
8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-1-[2-(2-methoxy-phenyl)-2-oxo-ethyl]-3-methyl-3,7-dihydro-purine-2,6-dione (**63**)



HPLC-MS (Method A3): *m/z* = 582 (M+1), R_t =4.20 min.

Example 64 (General procedure (D))

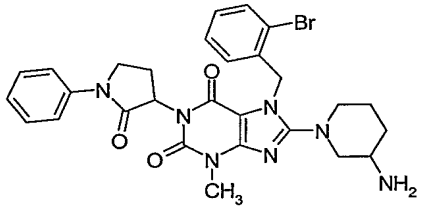
8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-3-methyl-1-(2-oxo-butyl)-3,7-dihydro-purine-2,6-dione (**64**)



HPLC-MS (Method A3): *m/z* = 504 (M+1), R_t =0.90 min.

Example 65 (General procedure (D))

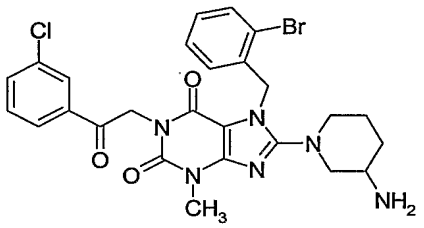
8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-3-methyl-1-(2-oxo-1-phenyl-pyrrolidin-3-yl)-3,7-dihydro-purine-2,6-dione (**65**)



HPLC-MS (Method A3): *m/z* = 593 (M+1), R_t =4.00 min.

Example 66 (General procedure (D))

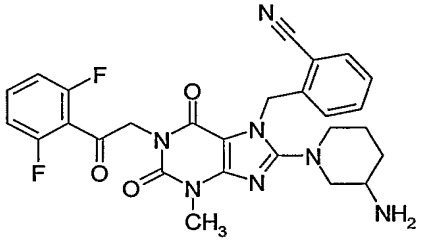
8-(3-Amino-piperidin-1-yl)-7-(2-bromo-benzyl)-1-[2-(3-chloro-phenyl)-2-oxo-ethyl]-3-methyl-3,7-dihydro-purine-2,6-dione (**66**)



HPLC-MS (Method A3): *m/z* = 586 (M+1), R_t =4.60 min.

Example 67 (General procedure (D))

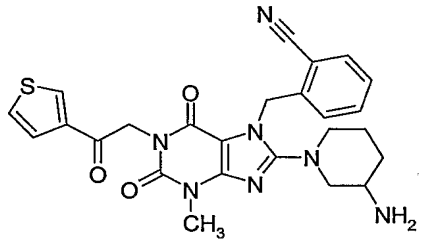
2-{8-(3-Amino-piperidin-1-yl)-1-[2-(2,6-difluoro-phenyl)-2-oxo-ethyl]-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-ylmethyl}-benzonitrile (**67**)



HPLC-MS (Method A3): *m/z* = 534(M+1), R_t =3.90 min.

Example 68 (General procedure (D))

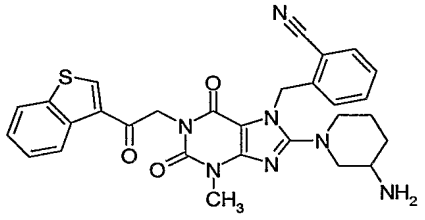
2-[8-(3-Amino-piperidin-1-yl)-3-methyl-2,6-dioxo-1-(2-oxo-2-thiophen-3-yl-ethyl)-1,2,3,6-tetrahydro-purin-7-ylmethyl]-benzonitrile (**68**)



HPLC-MS (Method A3): *m/z* = 504 (M+1), R_t =0.90 min.

Example 69 (General procedure (D))

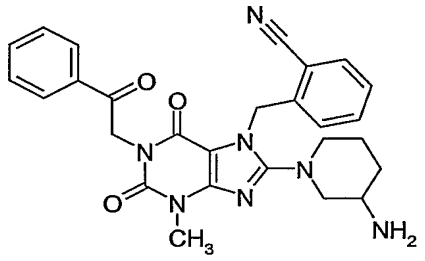
2-[8-(3-Amino-piperidin-1-yl)-1-(2-benzo[*b*]thiophen-3-yl-2-oxo-ethyl)-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-ylmethyl]-benzonitrile (**69**)



HPLC-MS (Method A3): *m/z* = 554 (M+1), R_t = 4.30 min.

Example 70 (General procedure (D))

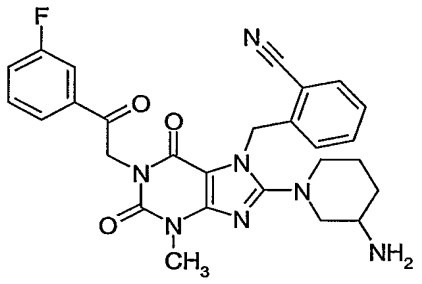
2-[8-(3-Amino-piperidin-1-yl)-3-methyl-2,6-dioxo-1-(2-oxo-2-phenyl-ethyl)-1,2,3,6-tetrahydro-purin-7-ylmethyl]-benzonitrile (**70**)



HPLC-MS (Method A3): *m/z* = 498 (M+1), R_t =3.60 min.

Example 71 (General procedure (D))

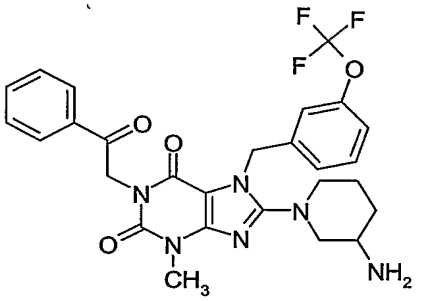
2-{8-(3-Amino-piperidin-1-yl)-1-[2-(3-fluoro-phenyl)-2-oxo-ethyl]-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-ylmethyl}-benzonitrile (**71**)



HPLC-MS (Method A3): *m/z* = 516 (M+1), R_t =3.80 min.

Example 72 (General procedure (D))

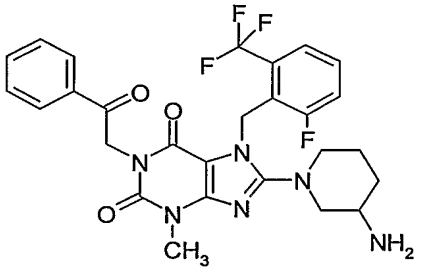
8-(3-Amino-piperidin-1-yl)-3-methyl-1-(2-oxo-2-phenyl-ethyl)-7-(3-trifluoromethoxy-benzyl)-3,7-dihydro-purine-2,6-dione (**72**)



HPLC-MS (Method A3): *m/z* = 557 (M+1), R_t =4.50 min.

Example 73 (General procedure (D))

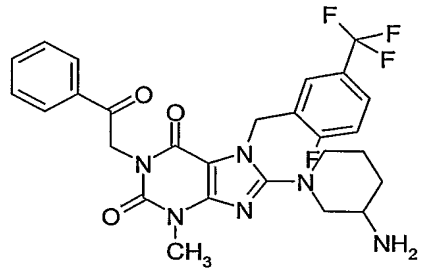
8-(3-Amino-piperidin-1-yl)-7-(2-fluoro-6-trifluoromethyl-benzyl)-3-methyl-1-(2-oxo-2-phenyl-ethyl)-3,7-dihydro-purine-2,6-dione (**73**)



HPLC-MS (Method A3): *m/z* = 559 (M+1), R_t =4.10 min.

Example 74 (General procedure (D))

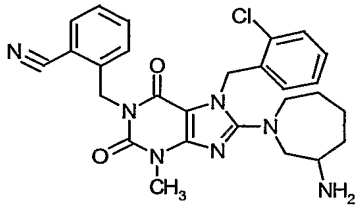
8-(3-Amino-piperidin-1-yl)-7-(2-fluoro-5-trifluoromethyl-benzyl)-3-methyl-1-(2-oxo-2-phenyl-ethyl)-3,7-dihydro-purine-2,6-dione (**74**)



HPLC-MS (Method A3): *m/z* = 559 (M+1), R_t =4.30 min.

Example 75

2-(8-(3-Aminoazepan-1-yl)-7-(2-chlorobenzyl)-3-methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-1-ylmethyl)benzonitrile. TFA (**75**)



Step A: 8-Bromo-7-(2-chlorobenzyl)-3-methyl-3,7-dihydropurine-2,6-dione. (75A)

8-Bromo-3-methyl-3,7-dihydropurine-2,6-dione and 2-chlorobenzyl bromide were reacted and purified as described in the General procedure G, step A, to afford compound (**75**A).

HPLC-MS (Method B): *m/z* = 371 (M+1), Rt 3.031 min.

Step B: 2-(8-Bromo-7-(2-chlorobenzyl)-3-methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-1-ylmethyl)benzonitrile (**75**B)

8-Bromo-7-(2-chlorobenzyl)-3-methyl-3,7-dihydropurine-2,6-dione (**75**A) and alpha-bromo-*o*-tolunitrile were reacted and purified as described in the General procedure G, Step B, to afford **75**B as white crystals.

Yield: 1.66 g (85%).

HPLC-MS (Method B): *m/z* = 486 (M+1), Rt = 4.733 min.

Step C: 2-(8-(3-Aminoazepan-1-yl)-7-(2-chlorobenzyl)-3-methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-1-ylmethyl)benzonitrile. TFA (**75**)

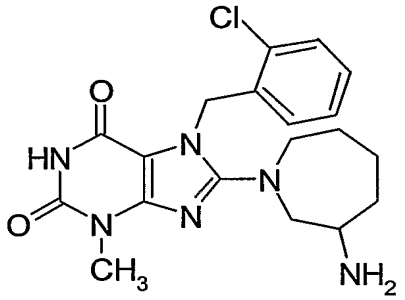
2-(8-Bromo-7-(2-chlorobenzyl)-3-methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-1-ylmethyl)benzonitrile (**75**B) (250 mg, 0.5 mmol) and azepan-3-ylamine (294 mg, 2.5 mmol), and triethylamine (0.35 ml, 2.5 mmol) were dissolved in 20 ml of DMSO and the mixture was subjected to microwaves (method F, 100°C, 300W) for five hours. To the reaction mixture was added 100 ml of water and 100 ml of dichloromethane, and the organic layer was separated and dried over sodium sulfate. The solvents were evaporated and the crude product was purified by preparative HPLC (method A1, Rt = 8.77 min.). Evaporation of the solvent afforded the title compound as an yellow oil.

Yield: 166 mg (51%).

HPLC-MS (Method B): *m/z* = 518 (M+), R_t = 3.09 min.

Example 76

8-(3-Aminoazepan-1-yl)-7-(2-chlorobenzyl)-3-methyl-3,7-dihydropurine-2,6-dione. TFA (**76**)



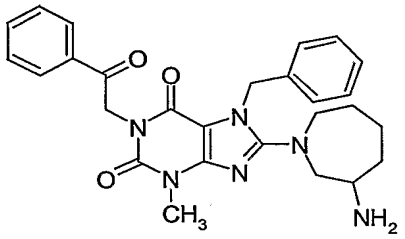
8-Bromo-7-(2-chlorobenzyl)-3-methyl-3,7-dihydropurine-2,6-dione (**75**A) (185 mg, 0.5 mmol) and azepan-3-ylamine (513 mg, 4.5 mmol), and triethylamine (0.35 ml, 2.5 mmol) were dissolved in 20 ml of DMSO and the mixture was subjected to microwaves (method F, 100°C, 300W) for four hours. To the reaction mixture was added 100 ml of water and 100 ml of dichloromethane, and the organic layer was separated and dried over magnesium sulfate. The solvents were evaporated and the crude product was purified by preparative HPLC (method A1, Rt = 7.12 min.). Evaporation of the solvent afforded the title compound as an yellow oil.

Yield: 110 mg (43%).

HPLC-MS (Method B): *m/z* = 403 (M+1), R_t = 1.87 min.

Example 77

8-(3-Aminoazepan-1-yl)-7-benzyl-3-methyl-1-(2-oxo-2-phenylethyl)-3,7-dihydropurine-2,6-dione. TFA (**77**)



Step A: 7-Benzyl-8-bromo-3-methyl-3,7-dihydropurine-2,6-dione (**77**A)

8-Bromo-3-methyl-3,7-dihydropurine-2,6-dione and benzyl bromide were reacted and purified as described in the General procedure G, step A, to afford **77**A.

HPLC-MS (Method B): *m/z* = 335 (M+)

Step B: 7-Benzyl-8-bromo-3-methyl-1-(2-oxo-2-phenylethyl)-3,7-dihydropurine-2,6-dione (**77**B)

7-Benzyl-8-bromo-3-methyl-3,7-dihydropurine-2,6-dione (**77**A) and 2-bromoacetophenone were reacted and purified as described in the General procedure G, Step B, to afford **77**B.

HPLC-MS (Method B): *m/z* = 453 (M+).

Step C: 8-(3-Aminoazepan-1-yl)-7-benzyl-3-methyl-1-(2-oxo-2-phenylethyl)-3,7-dihydropurine-2,6-dione. TFA (**77**)

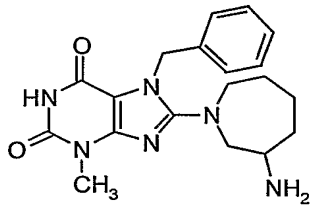
7-Benzyl-8-bromo-3-methyl-1-(2-oxo-2-phenylethyl)-3,7-dihydropurine-2,6-dione (**77**B) (227 mg, 0.5 mmol) and azepan-3-ylamine (342 mg, 3 mmol), and triethylamine (0.35 ml, 2.5 mmol) were dissolved in 20 ml of DMSO and the mixture was subjected to microwaves (method F, 100°C, 300W) for five hours. To the reaction mixture was added 100 ml of water and 100 ml of dichloromethane, and the organic layer was separated and dried over sodium sulfate. The solvents were evaporated and the crude product was purified by preparative HPLC (method A1, Rt = 8.77 min.). Evaporation of the solvent afforded the title compound as an yellow oil.

Yield: 130 mg (43%).

HPLC-MS (Method B): *m/z* = 487 (M+1), R_t = 2.97 min.

Example 78

8-(3-Aminoazepan-1-yl)-7-benzyl-3-methyl-3,7-dihydropurine-2,6-dione. TFA (**78**)



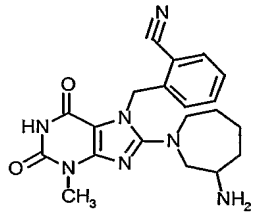
7-Benzyl-8-bromo-3-methyl-3,7-dihydropurine-2,6-dione (**77**A) (300 mg, 0.9 mmol) and azepan-3-ylamine (307 mg, 2.7 mmol), and triethylamine (0.62 ml, 4.5 mmol) were dissolved in NMP (3 ml) and the mixture was subjected to microwaves (method F, 200°C, 300W) for 30 minutes. To the reaction mixture was added 100 ml of water and 100 ml of dichloromethane, and the organic layer was washed with 1N NaOH, and dried over magnesium sulfate. The solvents were evaporated and the crude product was purified by preparative HPLC (method A1, Rt = 6.53 min.). Evaporation of the solvent afforded the title compound as an brown oil.

Yield: 30 mg (7%).

HPLC-MS (Method B): *m/z* = 369 (M+1), R_t = 1.53 min.

Example 79

2-(8-(3-Aminoazepan-1-yl)-3-methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl)benzonitrile. TFA (**79**)



Step A: 2-(8-Bromo-3-methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl)benzonitrile. (**79**A)

8-Bromo-3-methyl-3,7-dihydropurine-2,6-dione and alpha-bromo-*o*-tolunitrile were reacted and purified as described in the General procedure G, step A, to afford **79**A as white crystals in 91% yield.

HPLC-MS (Method B): *m/z* = 360 (M+1), Rt = 2.54 min.

Step B: 2-(8-(3-Aminoazepan-1-yl)-3-methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl)benzonitrile. TFA (**79**)

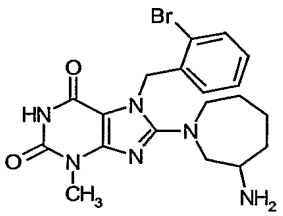
2-(8-Bromo-3-methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl)benzonitrile (**79**A) (181 mg, 0,5 mmol) and azepan-3-ylamine (342 mg, 3 mmol), and triethylamine (0.35 ml, 2.5 mmol) were dissolved in 20 ml of DMSO and the mixture was subjected to microwaves (method F, 100°C, 300W) for four hours. To the reaction mixture was added 100 ml of water and 100 ml of dichloromethane, and the organic layer was separated and dried over sodium sulfate. The solvents were evaporated and the crude product was purified by preparative HPLC (method A1, Rt = 6.22 min.). Evaporation of the solvent afforded the title compound as an yellow oil.

Yield: 142 mg (56%).

HPLC-MS (Method B): *m/z* = 394 (M+1), R_t = 1.41 min.

Example 80

8-(3-Aminoazepan-1-yl)-7-(2-bromobenzyl)-3-methyl-3,7-dihydropurine-2,6-dione. TFA (**80**)



Step A: 8-Bromo-7-(2-bromobenzyl)-3-methyl-3,7-dihydropurine-2,6-dione (**80**A)

8-Bromo-3-methyl-3,7-dihydropurine-2,6-dione and 2-bromobenzyl bromide were reacted and purified as described in the General procedure G, step A, to afford **80**A.

HPLC-MS (Method B): *m/z* = 414 (M+), Rt = 3.285 min.

Step B: 8-(3-Aminoazepan-1-yl)-7-(2-bromobenzyl)-3-methyl-3,7-dihydropurine-2,6-dione. TFA (**80**)

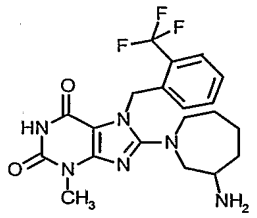
8-Bromo-7-(2-bromobenzyl)-3-methyl-3,7-dihydropurine-2,6-dione (**80**A) (300 mg, 0,7 mmol) and azepan-3-ylamine (248 mg, 2,2 mmol), and triethylamine (0.5 ml, 3,6 mmol) were dissolved in 3 ml of DMSO and the mixture was subjected to microwaves (method F, 200°C, 300W) for 30 minutes. To the reaction mixture was added 100 ml of water and 100 ml of dichloromethane, and the organic layer was separated and dried over sodium sulfate. The solvents were evaporated and the crude product was purified by preparative HPLC (method A1, Rt = 7.17 min.). Evaporation of the solvent afforded the title compound as an brown oil.

Yield: 138 mg (34%).

HPLC-MS (Method B): *m/z* = 447 (M+), R_t = 1.82 min.

Example 81

8-(3-Aminoazepan-1-yl)-3-methyl-7-(2-trifluoromethylbenzyl)-3,7-dihydropurine-2,6-dione. TFA (**81**)



Step A: 8-Bromo-3-methyl-7-(2-trifluoromethylbenzyl)-3,7-dihydropurine-2,6-dione (**81**A)

8-Bromo-3-methyl-3,7-dihydropurine-2,6-dione and 2-(trifluoromethyl)benzyl bromide were reacted and purified as described in the General procedure G, step A, to afford **81**A as white crystals in 69% yield.

HPLC-MS (Method B): *m/z* = 403 (M+), Rt = 3.54 min.

Step B: 8-(3-Aminoazepan-1-yl)-3-methyl-7-(2-trifluoromethylbenzyl)-3,7-dihydropurine-2,6-dione TFA (**81**)

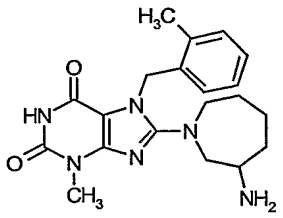
8-Bromo-3-methyl-7-(2-trifluoromethylbenzyl)-3,7-dihydropurine-2,6-dione (**81**A) (300 mg, 0,7 mmol) and azepan-3-ylamine (255 mg, 2,2 mmol), and triethylamine (0.5 ml, 3,7 mmol) were dissolved in 3 ml of DMSO and the mixture was subjected to microwaves (method F, 200°C, 300W) for 10 minutes. To the reaction mixture was added 100 ml of water and 100 ml of dichloromethane, and the organic layer was washed with 1N NaOH, and dried over sodium sulfate. The solvents were evaporated and the crude product was purified by preparative HPLC (method A1, Rt = 7.42 min.). Evaporation of the solvent afforded the title compound as a brown oil.

Yield: 96 mg (23%).

HPLC-MS (Method B): *m/z* = 437 (M+1), R_t = 2.30 min.

Example 82

8-(3-Aminoazepan-1-yl)-3-methyl-7-(2-methylbenzyl)-3,7-dihydropurine-2,6-dione. TFA (**82**)



Step A: 8-Bromo-3-methyl-7-(2-methylbenzyl)-3,7-dihydropurine-2,6-dione (**82**A)

8-Bromo-3-methyl-3,7-dihydropurine-2,6-dione and 2-methylbenzyl bromide were reacted and purified as described in the General procedure G, step A, to afford **82**A as white crystals in 79%.

HPLC-MS (Method B): *m/z* = 351 (M+2), Rt = 3.14 min.

Step B: 8-(3-Aminoazepan-1-yl)-3-methyl-7-(2-methylbenzyl)-3,7-dihydropurine-2,6-dione. TFA (**82**)

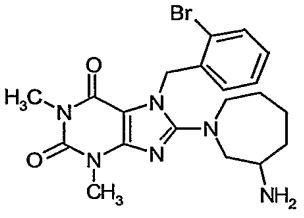
8-Bromo-3-methyl-7-(2-methylbenzyl)-3,7-dihydropurine-2,6-dione (**82**A) (300 mg, 0,86 mmol) and azepan-3-ylamine (294 mg, 2,6 mmol), and triethylamine (0.6 ml, 4.3 mmol) were dissolved in 3 ml of DMSO and the mixture was subjected to microwaves (method F, 200°C, 300W) for 3 minutes. To the reaction mixture was added 100 ml of water and 100 ml of dichloromethane, and the organic layer was washed with 1N NaOH, and dried over sodium sulfate. The solvents were evaporated and the crude product was purified by preparative HPLC (method A1, Rt = 6.93 min.). Evaporation of the solvent afforded the title compound as yellow crystals.

Yield: 201 mg (47%).

HPLC-MS (Method B): *m/z* = 383 (M+1), R_t = 2.06 min.

Example 83

8-(3-Aminoazepan-1-yl)-7-(2-bromobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione. TFA (**83**)



Step A: 7-(2-Bromobenzyl)-8-chloro-1,3-dimethyl-3,7-dihydropurine-2,6-dione (**83**A)

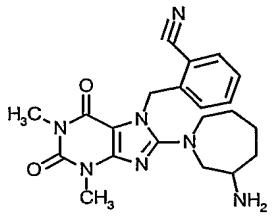
8-Chlorotheophylline and 2-bromobenzyl bromide were reacted and purified as described in the General procedure CC, step A, to afford **83**A as white crystals in 57%.
HPLC-MS (Method B): m/z = 385 (M+2), Rt = 3.77 min.

Step B: 8-(3-Aminoazepan-1-yl)-7-(2-bromobenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione TFA (**83**)

7-(2-Bromobenzyl)-8-chloro-1,3-dimethyl-3,7-dihydropurine-2,6-dione (**83**A) (300 mg, 0,8 mmol) and azepan-3-ylamine (268 mg, 2,3 mmol), and triethylamine (0.5 ml, 3.9 mmol) were dissolved in 3 ml of DMSO and the mixture was subjected to microwaves (method F, 200°C, 300W) for 15 minutes. To the reaction mixture was added 100 ml of water and 100 ml of dichloromethane, and the organic layer was washed with 1N NaOH, and dried over sodium sulfate. The solvents were evaporated and the crude product was purified by preparative HPLC (method A1, Rt = 7.76 min.). Evaporation of the solvent afforded the title compound as a brown oil.
Yield: 243 mg (54%).
HPLC-MS (Method B): *m/z* = 461 (M+), R_t = 2.32 min.

Example 84

2-[8-(3-Aminoazepan-1-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl]benzonitrile. TFA (**84**)



Step A: 7-(2-Bromobenzyl)-8-chloro-1,3-dimethyl-3,7-dihydropurine-2,6-dione (**84**A)

8-Chlorotheophylline and alpha-bromo-*o*-tolunitrile were reacted and purified as described in the General procedure C, step A, to afford (**84**A) as white crystals in 66%.
HPLC-MS (Method B): m/z = 330 (M+1), Rt = 2.93 min.

Step B: 2-[8-(3-Aminoazepan-1-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl]benzonitrile TFA (**84**)

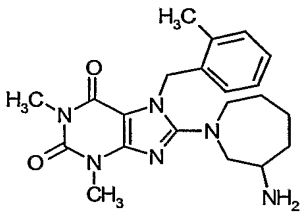
7-(2-Bromobenzyl)-8-chloro-1,3-dimethyl-3,7-dihydropurine-2,6-dione (**84**A) (300 mg, 0,9 mmol) and azepan-3-ylamine (312 mg, 2,7 mmol), and triethylamine (0.6 ml, 4.6 mmol) were dissolved in 3 ml of DMSO and the mixture was subjected to microwaves (method F, 200°C, 300W) for 30 minutes. To the reaction mixture was added 100 ml of water and 100 ml of dichloromethane, and the organic layer was washed with 1N NaOH, and dried over sodium sulfate. The solvents were evaporated and the crude product was purified by preparative HPLC (method A1, Rt = 6.76 min.). Evaporation of the solvent afforded the title compound as a brown oil.

Yield: 268 mg (56%).

HPLC-MS (Method B): *m/z* = 408 (M+1), R_t = 1.95 min.

Example 85

8-(3-Aminoazepan-1-yl)-1,3-dimethyl-7-(2-methylbenzyl)-3,7-dihydropurine-2,6-dione. TFA (**85**)



Step A: 8-Chloro-1,3-dimethyl-7-(2-methylbenzyl)-3,7-dihydropurine-2,6-dione (**85**A)

8-Chlorotheophylline and 2-methylbenzyl bromide were reacted and purified as described in the General procedure C, step A, to afford **85**A as white crystals in 86%.

HPLC-MS (Method B): m/z = 319 (M+1), Rt = 3.76

Step B: 8-(3-Aminoazepan-1-yl)-1,3-dimethyl-7-(2-methylbenzyl)-3,7-dihydropurine-2,6-dione. TFA (**85**)

8-Chloro-1,3-dimethyl-7-(2-methylbenzyl)-3,7-dihydropurine-2,6-dione (**85**A) (300 mg, 0,9 mmol) and azepan-3-ylamine (322 mg, 2,8 mmol), and triethylamine (0.7 ml, 4.7 mmol) were dissolved in 3 ml of DMSO and the mixture was subjected to microwaves (method F, 200°C, 300W) for 10 minutes. To the reaction mixture was added 100 ml of water and 100 ml of dichloromethane, and the organic layer was washed with 1N NaOH, and dried over sodium sulfate. The solvents were evaporated and the crude product was purified by

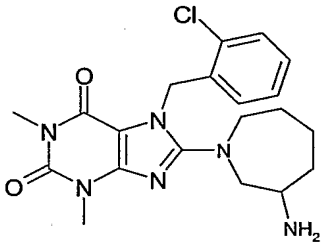
preparative HPLC (method A1, Rt = 7.5 min.). Evaporation of the solvent afforded the title compound as a brown oil.

Yield: 312 mg (65%).

HPLC-MS (Method B): *m/z* = 397 (M+1), R_t = 2.04 min.

Example 86

8-(3-Amino-azepan-1-yl)-7-(2-chloro-benzyl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione, TFA (**86**)



8-Chloro-7-(2-chloro-benzyl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione (0.34g, 1 mmol), azepan-3-ylamine (0.34g, 3 mmol), TEA (0.51g, 5 mmol) were mixed in 2-propanol (20 ml) and the mixture was subjected to microwaves (method F,120 °C) for 4 hours. The reaction mixture was evaporated and purified twice by preparative HPLC (method A1) to give the title compound as white crystals.

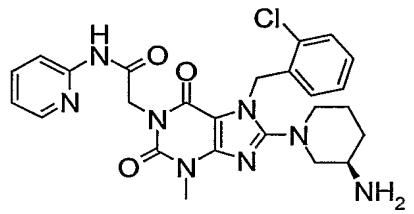
Yield: 340mg (64 %).

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 9.3 (br s, 1H), 8.6 (br s, 2H), 7.4 (m, 1H), 7.2 (m, 2H), 6.9 (m,1H), 5.5 (q, 2H), 3.9 (m, 1H), 3.55-3.75 (m, 3H), 3.45 (s, 3H), 3.3 (s, 3H), 2.9 (m, 1H), 2.25 (m, 1H), 1.85 (m, 1H), 1.6 (m, 2H), 1.3 (m, 2H).

^{13}C-NMR($CDCl_3$) δ: 155.04, 154.42, 151.73, 133.87, 131.98, 130.07, 129.56, 127.80, 126.81, 105.51, 55.15, 54.18, 51.70, 48.11, 31.18, 30.79, 30.07, 28.25, 22.42.

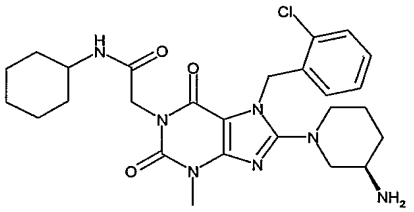
Example 87 (General procedure (H))

(R) 2-[8-(3-Amino-piperidin-1-yl)-7-(2-chloro-benzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-pyridin-2-yl-acetamide



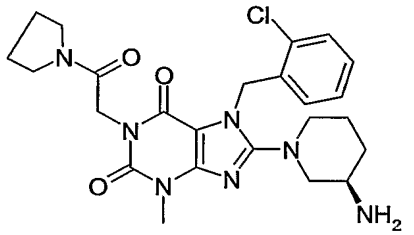
^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 10.80 (s, 1H), 8.32(s, 1H), 7.95(s, 4H), 7.75(s, 1H), 7.51(s, 1H), 7.31(s, 2H), 7.10(s, 1H), 6.87(s, 1H), 5.40(s, 2H), 4.65(s, 2H), 3.61(s, 1H), 3.45(s, 3H), 3.31(s, 1H), 3.13(s, 2H), 2.87(s, 1H), 2.43(s, 1H), 1.93(s, 1H), 1.73(s, 1H), 1.50(s, 2H).
HPLC-MS (Method B): *m/z* = 535 (M+1), Rt = 2.059 min.

Example 88 (General procedure (H))
(R) 2-[8-(3-Amino-piperidin-1-yl)-7-(2-chloro-benzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-cyclohexyl-acetamide



^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.95 (br, 3H), 7.83 (d, 1H), 7.51 (m, 1H), 7.24-7.37 (m, 1H), 6.86 (d, 1H), 5.39 (s, 2H), 4.33 (s, 2H), 3.59 (d, 1H), 3.47 (s, 3H), 3.31-3.40 (m, 3H), 1.89-1.97 (m, 1H), 1.59-1.79 (m, 2.5H), 1.42-1.59 (m, 2.5H), 1.04-1.30 (m, 6H)

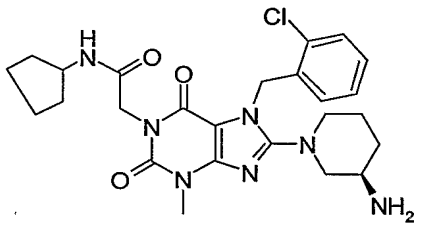
Example 89 (General procedure (H))
(R) 8-(3-Amino-piperidin-1-yl)-7-(2-chloro-benzyl)-3-methyl-1-(2-oxo-2-pyrrolidin-1-yl-ethyl)-3,7-dihydro-purine-2,6-dione



^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.95 (br, 3H), 7.50 (d, 1H), 7.31 (m, 2H), 6.83 (d, 1H), 5.38 (s, 2H), 4.50 (s, 2H), 3.59 (d, 1H), 3.42-3.50 (m, 4H), 3.31-3.42 (br, 2H), 3.30 (s,1H), 3.22-3.28 (m, 1H), 3.08-3.18 (m, 2H), 2.99 (s, 1H), 2.83-2.92 (m, 1H), 1.85-1.97 (m, 2.5H), 1.70-1.81 (m, 2.5H), 1.43-1.58 (m, 2H)

Example 90 (General procedure (H))

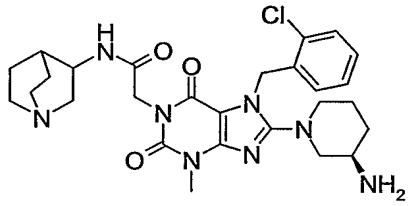
(R) 2-[8-(3-Aminopiperidin-1-yl)-7-(2-chlorobenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-cyclopentylacetamide. TFA



^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.96 (s, 4H), 7.52 (d, 1H), 7.25-7.38 (m, 2H), 6.83 (d, 1H), 5.40 (s, 2H), 4.33 (s, 2H), 3.92 (q, 1H), 3.42 (s, 3H), 3.25-3.37 (m, 1H), 3.05-3.17 (m, 2H), 2.85 (t, 1H), 1.88-1.96 (m, 1H), 1.70-1.81 (m, 4H), 1.56-1.70 (m, 3H), 1.42-1.55 (m, 5H), 1.30-1.40 (m,3H).

Example 91 (General procedure (H))

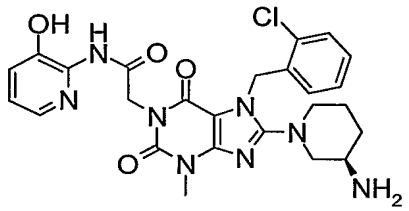
2-[8-(3-(R) Amino-piperidin-1-yl)-7-(2-chloro-benzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-N-(1-aza-bicyclo[2.2.2]oct-3-yl)-acetamide



^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.50 (s, 1H), 8.41 (d, 1H), 7.99 (br, 3H), 7.50 (d, 1H), 7.23-7.39 (m, 2H), 6.83 (d, 1H), 5.41 (s, 2H), 4.43 (dd, 2H), 4.03 (m, 1H), 3.54-3.64 (m, 1H), 3.31-3.51 (br, 6H), 3.31 (s, 1H), 3.05-3.25 (m, 4H), 2.98 (s, 1H), 2.81-2.93 (m, 1H), 1.62-2.10 (m, 6H), 1.41-1.58 (m, 2H), 1.13-1.27 (m, 1H)

Example 92 (General procedure (H))

(R) 2-[8-(3-Amino-piperidin-1-yl)-7-(2-chloro-benzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-(3-hydroxy-pyridin-2-yl)-acetamide

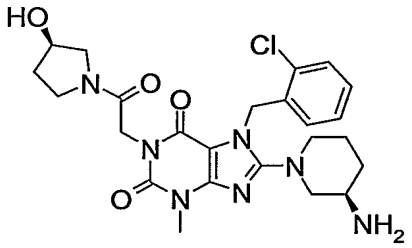


^{1}H-NMR (MeOD, 300 MHz) δ: 7.865 (d, 1H), 7.505 (d, 1H), 7.40 - 7.22 (m, 3H), 7.16 - 7.08 (m, 1H), 6.91 - 6.84 (m, 1H), 5.40 (s, 2H), 4.75 (s, 2H), 6.65 - 3.54 (m, 1H), 3.45 (s, 3H), 3.18 - 3.04 (m, 3H), 2.92 - 2.79 (m, 1H), 1.97 - 1.86 (m, 1H), 1.82 - 1.65 (m, 1H), 1.60 - 1.40 (m, 2H).

HPLC-MS (Method B): *m/z* = 539 (M+1) Rt = 1.836 min.:

Example 93 (General procedure (H))

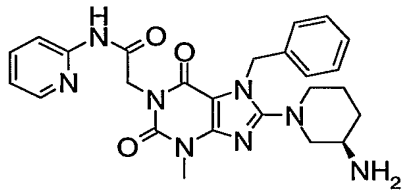
(R,R) 8-(3-Amino-piperidin-1-yl)-7-(2-chloro-benzyl)-1-[2-(3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-3-methyl-3,7-dihydro-purine-2,6-dione



^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7,95 (br, 3H), 7.50 (d, 1H), 7.25-7.38 (m, 2H), 6.84 (d, 1H), 5.38 (s, 2H), 4.39-4.62 (m, 2H), 4.51 (s, 0.5 H), 4.25 (s, 0.5H), 3.49-3.65 (m, 2H), 3.45 (s, 3H), 3.07-3.31 (m, 3H), 2.99 (s, 1H), 2.83-2.92 (m, 1H), 1.69-2.01 (m, 3H), 1.43-1.58 (m, 2H)

Example 94 (General procedure (H))

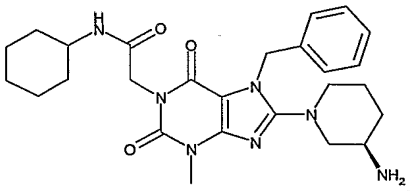
(R) 2-[8-(3-Amino-piperidin-1-yl)-7-benzyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-pyridin-2-yl-acetamide



^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 10.77 (s, 1H), 8.32 (s, 1H), 7.95 (br, 3H), 7.71-7.85 (m, 1H), 7.23-7.39 (m, 4H), 7.13-7.23 (m, 2H), 7.06-7.13 (m, 1H), 5.37 (s, 2H), 4.70 (s, 2H), 3.54-3.65 (m, 1H), 3.12-3.26 (m, 1H), 3.02-3.12 (m, 1H), 2.98 (s, 1H), 2.80-2.95 (m, 1H), 1.90-2.00 (m, 1H), 1.70-1.82 (m, 1H), 1.45-1.61 (m, 2H)

Example 95 (General procedure (H))

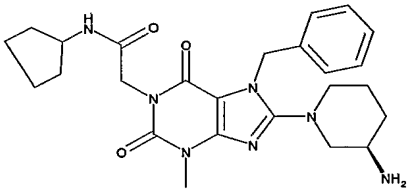
(R) 2-[8-(3-Amino-piperidin-1-yl)-7-benzyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-cyclohexyl-acetamide



^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.96 (s, 3H), 7.85 (d, 1H), 7.24-7.40 (m, 3H), 7.18 (d, 2H), 5.36 (s, 2H), 4.37 (s, 2H), 3.53-3.62 (m, 1H), 3.40 (s, 3H), 3.11-3.24 (m, 1H), 3.00-3.11 (m, 1H), 2.97 (s, 1H), 2.79 (m, 1H), 1.89-2.01 (m, 1H), 1.61-1.82 (m, 5H), 1.44-1.61 (m, 3H), 1.05-1.31 (m, 6H)

Example 96 (General procedure (H))

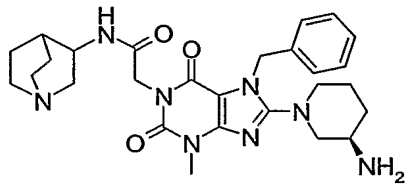
(R) 2-[8-(3-Amino-piperidin-1-yl)-7-benzyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-cyclopentyl-acetamide



^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.87-8.03 (m, 4H), 7.24-7.39 (m, 3H), 7.18 (d, 2H), 5.37 (s, 2H), 4.37 (s, 2H), 3.91-4.00 (m, 1H), 3.57 (d, 1H), 3.40 (s, 3H), 3.12-3.23 (m, 1H), 3.01-3.10 (m, 1H), 2.99 (s, 1H), 2.79-2.88 (m, 1H), 1.90-2.01 (m, 1H), 1.70-1.84 (m, 2H), 1.56-1.70 (m, 2H), 1.42-1.56 (m, 4H), 1.30-1.42 (m, 2H).

Example 97 (General procedure (H))

2-[8-(3-(R)-Amino-piperidin-1-yl)-7-benzyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-(1-aza-bicyclo[2.2.2]oct-3-yl)-acetamide

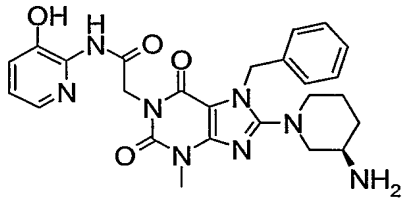


^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.48 (br, 1H), 8.43 (d, 1H), 7.98 (br, 3H), 7.24-7.38 (m, 3H), 7.17 (d, 2H), 5.36 (s, 2H), 4.47 (dd, 2H), 4.05 (br, 1H), 3.54-3.66 (m, 2H), 3.40 (s, 3H), 3.11-

3.26 (m, 4H), 3.00-3.11 (m, 1H), 2.99 (s, 1H), 2.88-2.97 (m, 1H), 2.79-2.88 (m, 1H), 1.91-2.08 (m, 3H), 1.64-1.91 (m, 3H), 1.45 (m, 2H)

Example 98 (General procedure (H))

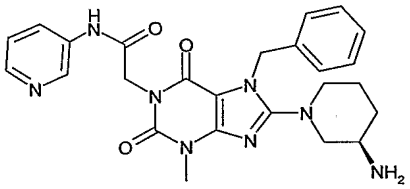
(R) 2-[8-(3-Amino-piperidin-1-yl)-7-benzyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-(3-hydroxy-pyridin-2-yl)-acetamide



^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.76 (br, 3H), 7.89 (d, 1H), 7.24-7.40 (m, 5H), 7.13-7.24 (m, 3H), 5.38 (s, 2H), 4.82 (s, 2H), 3.56-3.65 (m, 1H), 3.40 (s, 3H), 3.14-3.23 (m, 1H), 3.02-3.11 (m, 1H), 2.99 (s, 1H), 2.80-2.93 (m, 1H), 1.91 (m, 1H), 1.71-1.83 (m, 1H), 1.46-1.60 (m, 2H)

Example 99 (General procedure (H))

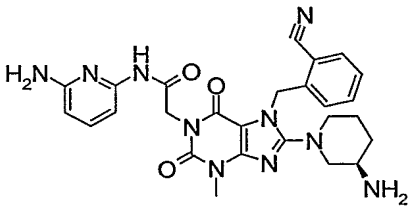
(R) 2-[8-(3-Amino-piperidin-1-yl)-7-benzyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-pyridin-3-yl-acetamide



^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 10.52 (br, 1H), 8.76 (s, 1H), 8.31 (d, 1H), 7.85-8.05 (m, 5H), 7.56-7.70 (m, 2H), 7.38-7.46 (m, 1H), 7.24-7.38 (m, 3H), 7.19 (d, 2H), 5.38 (s, 2H), 4.67 (s, 2H), 3.52 (m, 1H), 3.45 (s, 3H), 3.13-3.25 (m, 1H), 3.01-3.13 (m, 1H), 2.98 (s, 1H), 2.81-2.94 (m, 1H), 1.90-2.01 (m, 1H), 1.70-1.82 (m, 1H), 1.45-1.61 (m, 2H)

Example 100 (General procedure (H))

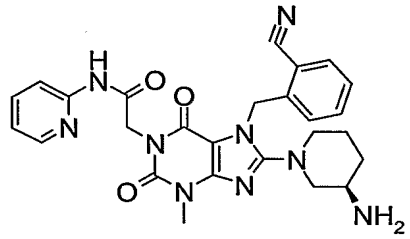
(R) 2-[8-(3-Amino-piperidin-1-yl)-7-(2-cyano-benzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-(6-amino-pyridin-2-yl)-acetamide



^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.85-8.02 (m, 4H), 7.59-7.68 (m, 1H), 7.45-7.55 (m, 1H), 7.32-7.43 (m, 1H), 7.07 (d, 1H), 6.18-6.24 (m, 1H), 5.53 (s, 2H), 4.49 (s, 2H), 3.57 (m, 1H), 3.44 (s, 3H), 3.29 (s, 1H), 3.07-3.23 (m, 2H), 2.95 (s, 3H), 2.94-2.88 (M, 1H), 1.89 (m, 1H), 1.74-1.85 (m, 1H), 1.49 (m, 2H)

Example 101 (General procedure (H))

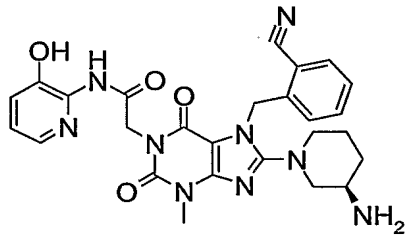
(R) 2-[8-(3-Amino-piperidin-1-yl)-7-(2-cyano-benzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-pyridin-2-yl-acetamide



^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 10.74 (s, 1H), 8.32 (s, 1H), 7.83-8.05 (m, 5H), 7.70-7.83 (m, 1H), 7.59-7.70 (m, 1H), 7.45-7.59 (m, 1H), 7.03-7.17 (m, 2H), 5.54 (s, 2H), 4.64 (s, 2H), 3.54-3.69 (m, 1H), 3.40 (s, 3H), 3.18-3.50 (m, 4H), 3.0 (s, 3H), 1.87 (m, 1H), 1.70-1.87 (m, 1H), 1.47-1.64 (m, 2H).

Example 102 (General procedure (H))

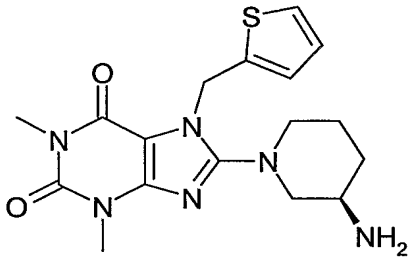
(R) 2-[8-(3-Amino-piperidin-1-yl)-7-(2-cyano-benzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl]-*N*-(3-hydroxy-pyridin-2-yl)-acetamide



^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.96 (br, 3H), 7.84-7.90 (m, 2H), 7.65 (t, 1H), 7.49 (t, 1H), 7.32 (d, 1H), 7.13-7.19 (m, 1H), 7.08 (d, 1H), 5.52 (s, 2H), 4.75 (s, 2H), 3.53-3.61 (m, 1H), 3.40 (s, 3H), 3.08-3.23 (m, 2H), 3.05 (s, 2H), 2.90-3.05 (M, 1H), 1.90-2.00 (m, 1H), 1.72-1.84 (m, 1H), 1.48-1.65 (m, 2H)

Example 103 (General procedure (E))

(R) 8-(3-Amino-piperidin-1-yl)-1,3-dimethyl-7-thiophen-2-ylmethyl-3,7-dihydro-purine-2,6-dione



^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 8.40 (br. 3H), 7.18 (d, 1H), 7.03 (d, 1H), 6.88 (m, 1H), 5.5 (s, 2H), 3.70 - 3.55 (m, 2H), 3.45 (s, 3H), 3.37 (s, 3H), 3.30 - 3.00 (m, 3H), 2.20 - 1.55 (m, 4H). ^{13}C-NMR (CDCl3, 200 MHz) δ:155.15, 154.73, 151.60, 147.04, 138.04, 127.08, 127.01, 126.18, 104.75, 52.16, 51.44, 46.71, 43.53, 29.73, 27.99, 27.65, 21.07.

METHOD OF PREPARING SALTS

General Prodedure I for preparation of succinate and hemisuccinate salts:

A compound of the general formula I is suspended or dissolved in an appropriate solvent or a mixture of solvents. The mixture is eventually heated to 40-120°C depending on the boiling point of the appropriate solvent or solvent mixture so that the solution becomes clear. The solution can be filtered before one (if the succinate is desired) or half (if the hemisuccinate is desired) an equivalent of succinic acid is added, as a solid or dissolved in an appropriate solvent or a mixture of solvents. The succinic acid can also be added before a clear solution of the compound is obtained. Crystallisation can be achieved by distilling off solvent, or slowly cooling the solution, or adding the solution to a third solvent or mixture of solvents, or adding solvent or a mixture of solvents to the solution or combinations thereof. The succinate or hemisuccinate salt is isolated by filtration or centrifugation?, washed with the appropriate solvent or mixture of solvents and drying to constant weight.

Examples of solvents include but are not limited to: water, hydrocarbons (aromatic, aliphatic, unsaturated, aromatic) such as pentane, heptane, cumene or toluene; alcohols (monohydric or polyhydric aliphatic, unsaturated, aromatic) such as methanol, ethanol, 1-propanol, 2-propanol, 2-methyl-1-propanol, 1-butanol, 2-butanol, 1-pentanol; ethers (open chain or cyclic) such as ethyl ether, tert-butyl methyl ether, anisole, 1,4-dioxane or tetrahydrofurane; carbonyls (aldehydes, ketones) such as acetone, methyl ethyl ketone, methyl isobutyl

ketone; carbonic acids such as formic acid, acetic acid, carbonic acid; esters (mono or poly saturated aliphatic, unsaturated or aromatic) such as ethyl formiate, methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, tert butyl acetate; carbonates such as dimethylcarbonate; halogenated hydrocarbons such as dichloromethane; solvents containing nitrogen (nitriles, amines, nitro, amides ureas), oxosulfor compounds such as acetonitril, *N,N*- dimethylformamide, *N*-methyl-2-pyrrolidinone, sulfolane, dimethylsulfoxide, 1,3-dimethyl-3,4,5,6-tetrahydroxy-2(1H)-pyrimidinone or combinations thereof.

The process for the preparation of the various succinate and hemisuccinate salts of the present invention comprises:

a) suspending or dissolving compound of the general formula I in an appropriate solvent or a mixtures of solvents,

b) optionally heating the mixture to 40-120°C depending on the boiling point of the appropriate solvent or solvent mixture so that the solution becomes clear, and filtering the clear solution,

c) addition of one (if the succinate salt is desired)or a half equivalent succinic acids (if the hemisuccinate is desired) as a solid or dissolved in an appropriate solvent or a mixtures of solvents,

d) optionally the succinic acid is added before a clear solution of the compound of the general formula.... is obtained,

d) optionally adding a co solvent at 40-120°C,

e) optionally distilling off solvent,

f) slowly cooling the solution to 0-50°C, e.g. to 0-25°C, preferably to 0-5°C, or adding the solution to a third solvent or mixture of solvents, or adding solvent or a mixture of solvents to the solution or combinations thereof whereby crystals are formed,

g) filtrating the resulting suspension,

h) washing the filter cake with an appropriate solvent or mixture of solvents and drying the filter cake to constant weight.

Examples of solvents include but are not limited to: water, hydrocarbons (aromatic, aliphatic, unsaturated, aromatic) such as pentane, heptane, cumene or toluene; alcohols (monohydric or polyhydric aliphatic, unsaturated, aromatic) such as methanol, ethanol, 1-propanol, 2-propanol, 2-methyl-1-propanol, 1-butanol, 2-butanol, 1-pentanol; ethers (open chain or cyclic) such as ethyl ether, tert-butyl methyl ether, anisole, 1,4-dioxane or tetrahydrofurane; carbonyls (aldehydes, ketones) such as acetone, methyl ethyl ketone, methyl isobutyl

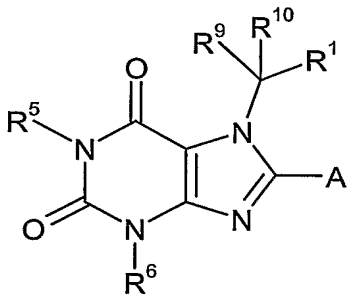
ketone; esters (mono or poly saturated aliphatic, unsaturated or aromatic) such as ethyl formiate, methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, tert butyl acetate; carbonates such as dimethylcarbonate; halogenated hydrocarbons such as dichloromethane; solvents containing nitrogen (nitriles, amines, nitro, amides ureas), oxosulfor compounds such as acetonitril, *N,N*- dimethylformamide, *N*-methyl-2-pyrrolidinone, sulfolane, dimethylsulfoxide, 1,3-dimethyl-3,4,5,6-tetrahydroxy-2(1H)-pyrimidinone or combinations thereof.

Example 104 (General procedure (I))
[(R) 8-(3-Aminopiperidin-1-yl)-1,3-dimethyl-7-(2-methylbenzyl)-3,7-dihydropurine-2,6-dione hemisuccinate]

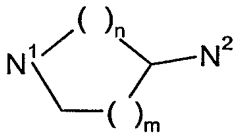
To a solution of 13.7 g (R) 8-(3-Aminopiperidin-1-yl)-1,3-dimethyl-7-(2-methylbenzyl)-3,7-dihydropurine-2,6-dione in 800 ml toluene warmed to 50°C was added a solution of 2.1 g succinic acid in 50 ml methanol. After initiation of the crystallisation was observed the mixture was allowed to cool to 15°C over 3 hours. (R) 8-(3-Aminopiperidin-1-yl)-1,3-dimethyl-7-(2-methylbenzyl)-3,7-dihydropurine-2,6-dione hemisuccinate was isolated by filtration, washed with toluene, and dried for 24 hours at 40°C. Yield: 13.95 g, 88%. Mp: 215°C.

Claims

1. Hemisuccinate salt of a compound of formula I



A =



Formula I

wherein

A may be attached at either N^1 or at N^2 to the purine system and

n is one or two,

m is one, two, or three,

R^1 is aryl optionally substituted with one or more R^2 independently or heteroaryl optionally substituted with one or more R^2 independently,

R^2 is H, C_1-C_7 alkyl, C_2-C_7 alkenyl, C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, -$NHCOR^3$, -$NHSO_2R^3$, -SR^3, -SOR^3, -SO_2R^3, -$OCOR^3$, -CO_2R^4, -$CON(R^4)_2$, -$CSN(R^4)_2$, -$NHCON(R^4)_2$, -$NHCSN(R^4)_2$, -$NHCONNH_2$, -$SO_2N(R^4)_2$, -OR^4, cyano, nitro, halogen, wherein each alkyl, alkenyl, alkynyl, cycloalkyl and cycloheteroalkyl is optionally substituted with one or more R^3 independently,

R^3 is Halogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_7 cycloalkyl, aryl, heteroaryl, -OR^{11}, -$N(R^{11})_2$, -SR^{11}, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl is substituted with one or more R^{11} independently,

R^4 is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, aryl-C_1-C_5 alkyl, heteroaryl, heteroaryl-C_1-C_5 alkyl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, aryl-C_1-C_5 alkyl, heteroaryl, and heteroaryl-C_1-C_5 alkyl is substituted with one or more R^{11} independently,

R^5 is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl-C_1-C_5 alkyl, C_3-C_7 cycloheteroalkyl, C_3-C_7 cycloheteroalkyl-C_1-C_5 alkyl, aryl, heteroaryl, aryl-C_1-C_5 alkyl, heteroaryl-C_1-C_5 alkyl, -OR^7, -$[(CH_2)_o$-$O]_p$-alkyl, wherein o and p are 1-3 independently, and wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-C_1-C_5 alkyl, cycloheteroalkyl, C_3-C_7 cycloheteroalkyl-C_1-C_5 alkyl, aryl, aryl-C_1-C_5 alkyl, heteroaryl, and heteroaryl-C_1-C_5 alkyl is optionally substituted with one or more substituents independently selected from R^7 or R^{11} independently,

R^6 is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, heteroaryl, aryl-C_1-C_5 alkyl, heteroaryl-C_1-C_5 alkyl, C_3-C_7 cycloheteroalkyl-C_1-C_5 alkyl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, C_3-C_7 cycloheteroalkyl-C_1-C_5 alkyl, aryl, aryl-C_1-C_5 alkyl, heteroaryl, aryl-C_1-C_5 alkyl, and heteroaryl-C_1-C_5 alkyl is optionally substituted with one or more R^{11} independently,

R^7 is H, =O, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, heteroaryl, -OR^{11}, -$N(R^{11})_2$, -SR^{11}, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, and heteroaryl is optionally substituted with one or more R^{11} independently,

R^8 is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, heteroaryl, -OR^{11}, -$N(R^{11})_2$, -SR^{11}, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, and heteroaryl is optionally substituted with one or more R^{11} independently,

R^9 and R^{10} is independently H, C_1-C_{10} alkyl optionally substituted with one or more R^8 independently, or halogen,

R^{11} is H, -CF_3, -CCl_3, -OCF_3, -OMe, cyano, halogen, -OH, -COMe, -$CONH_2$, -CONHMe, -$CONMe_2$, -NO_2, C_1-C_{10} alkyl, aryl, heteroaryl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, wherein each alkyl, cycloalkyl, cycloheteroalkyl, aryl, and heteroaryl is optionally substituted with one or more R^{12} independently,

R^{12} is H, C_1-C_{10} alkyl, -CF_3, -CCl_3, -OCF_3, -OMe, cyano, halogen, -OH, -COMe, -$CONH_2$, -CONHMe, -$CONMe_2$, -NH_2, -NO_2

If R^9 and R^{10} is C_1-C_{10} alkyl they may be connected to form a cyclopropyl ring,

if two R^4 or two R^{11} are attached to the same nitrogen they may be connected to form a 3- to 7-membered ring,

or any tautomeric form or any optical isomer or mixture of optical isomers, including a racemic mixture, or a salt thereof with a pharmaceutically acceptable acid or base.

2. Hemisuccinate salt according to claim 1 wherein R^1 is aryl optionally substituted with one or more R^2 independently.

3. Hemisuccinate salt according to claim 2 wherein R^1 is phenyl substituted with one or more R^2 independently.

4. Hemisuccinate salt according to claim 2 wherein R^1 is aryl.

5. Hemisuccinate salt according to claim 4 wherein R^1 is phenyl.

6. Hemisuccinate salt according to any one of the claims 1 to 5 wherein R^2 is C_1-C_7 alkyl, C_2-C_7 alkynyl, cyano, or halogen, wherein each alkyl and alkynyl is optionally substituted with one or more R^3 independently.

7. Hemisuccinate salt according to claim 6 wherein R^2 is C_1-C_7 alkyl, C_2-C_7 alkynyl, cyano, or halogen.

8. Hemisuccinate salt according to claim 7 wherein R^2 is methyl.

9. Hemisuccinate salt according to claim 7 wherein R^2 is cyano or halogen.

10. Hemisuccinate salt according to any one of the claims 1 to 9 wherein R^3 is C_1-C_{10} alkyl or aryl, wherein each alkyl or aryl is substituted with one or more R^{11} independently.

11. Hemisuccinate salt according to claim 10 wherein R^3 is C_1-C_{10} alkyl or aryl.

12. Hemisuccinate salt according to claim 11 wherein R^3 is methyl or phenyl.

13. Hemisuccinate salt according to any one of the claims 1 to 8 wherein R^3 is halogen

14. Hemisuccinate salt according to any one of the claims 1 to 12 wherein R^4 is H, C_1-C_{10} alkyl or aryl, wherein each alkyl or aryl is substituted with one or more R^{11} independently.

15. Hemisuccinate salt according to claim 14 wherein R^4 is H, C_1-C_{10} alkyl or aryl.

16. Hemisuccinate salt according to claim 15 wherein R^4 is H, methyl or phenyl.

17. Hemisuccinate salt according to any one of the claims 1 to 16 wherein R^5 is H, C_1-C_{10} alkyl, aryl-C_1-C_5 alkyl, or heteroaryl-C_1-C_5 alkyl, wherein each alkyl, aryl-C_1-C_5 alkyl and heteroaryl-C_1-C_5 alkyl is optionally substituted with one or more R^7 independently.

18. Hemisuccinate salt according to claim 17 wherein R^5 is H or C_1-C_{10} alkyl optionally substituted with one or more R^7 independently.

19. Hemisuccinate salt according to claim 18 wherein R^5 is H or C_1-C_{10} alkyl.

20. Hemisuccinate salt according to claim 19 wherein R^5 is H.

21. Hemisuccinate salt according to claim 19 wherein R^5 is methyl.

22. Hemisuccinate salt according to any one of the claims 1 to 21 wherein R^6 is C_1-C_{10} alkyl, aryl-C_1-C_5 alkyl, or heteroaryl-C_1-C_5 alkyl, wherein each alkyl, aryl-C_1-C_5 alkyl and heteroaryl-C_1-C_5 alkyl is optionally substituted with one or more R^{11} independently.

23. Hemisuccinate salt according to claim 22 wherein R^6 is C_1-C_{10} alkyl, aryl-C_1-C_5 alkyl, or heteroaryl-C_1-C_5 alkyl.

24. Hemisuccinate salt according to claim 22 wherein R^6 is C_1-C_{10} alkyl optionally substituted with one or more R^{11} independently.

25. Hemisuccinate salt according to claim 24 wherein R^6 is C_1-C_{10} alkyl.

26. Hemisuccinate salt according to claim 25 wherein R^6 is methyl.

27. Hemisuccinate salt according to any one of the claims 1 to 26 wherein R^7 is H, =O, aryl, heteroaryl, OR^{11}, $N(R^{11})_2$, SR^{11}, wherein each aryl and heteroaryl is optionally substituted with one or more R^{11} independently.

28. Hemisuccinate salt according to claim 27 wherein R^7 is H, =O, C_1-C_{10} alkyl, -OR^{11}, -$N(R^{11})_2$, -SR^{11} .

29. Hemisuccinate salt according to claim 28 wherein R^7 is H, =O, -OR^{11}, or -$N(R^{11})_2$

30. Hemisuccinate salt according to claim 29 wherein R^7 is H, =O, or -$N(R^{11})_2$

31. Hemisuccinate salt according to claim 30 wherein R^7 is =O or -$N(R^{11})_2$

32. Hemisuccinate salt according to any one of the claims 1 to 31 wherein R^8 is aryl or heteroaryl, wherein each aryl and heteroaryl is optionally substituted with one or more R^{11} independently.

33. Hemisuccinate salt according to claim 32 wherein R^8 is aryl or heteroaryl.

34. Hemisuccinate salt according to claim 33 wherein R^8 is phenyl.

35. Hemisuccinate salt according to any one of the claims 1 to 34 wherein R^9 is H, C_1-C_{10} alkyl, or halogen.

36. Hemisuccinate salt according claim 35 wherein R^9 is H.

37. Hemisuccinate salt according to any one of the claims 1 to 36 wherein R^{10} is H, C_1-C_{10} alkyl, or halogen.

38. Hemisuccinate salt according claim 37 wherein R^{10} is H.

39. Hemisuccinate salt according to any one of the claims 1 to 38 wherein R^{11} is H, -CF_3, cyano, halogen, -OH, -NO_2, C_1-C_{10} alkyl, aryl, heteroaryl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, wherein each alkyl, cycloalkyl, cycloheteroalkyl, aryl, and heteroaryl is optionally substituted with one or more R^{12} independently

40. Hemisuccinate salt according to claim 39 wherein R^{11} is H, halogen, -OH, C_1-C_{10} alkyl, aryl, heteroaryl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, wherein each alkyl, cycloalkyl,

cycloheteroalkyl, aryl, and heteroaryl is optionally substituted with one or more R^{12} independently.

41. Hemisuccinate salt according to claim 40 wherein R^{11} is H, halogen, $-CH_3$, aryl, heteroaryl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, wherein each alkyl, cycloalkyl, cycloheteroalkyl, aryl, and heteroaryl is optionally substituted with one or more R^{12} independently.

42. Hemisuccinate salt according to claim 41 wherein R^{11} is H, halogen, $-CH_3$, heteroaryl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, wherein each alkyl, cycloalkyl, cycloheteroalkyl, and heteroaryl is optionally substituted with one or more R^{12} independently

43. Hemisuccinate salt according to claim 42 wherein R^{11} is H, halogen, or $-CH_3$

44. Hemisuccinate salt according to claim 42 wherein R^{11} is heteroaryl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, wherein each cycloalkyl, cycloheteroalkyl,and heteroaryl is optionally substituted with one or more R^{12} independently

45. Hemisuccinate salt according to claim 44 wherein R^{11} is selected from the group consisting of pyridine, cyclopentane, cyclohexane, and pyrrolidine, wherein each cycloalkyl, cycloheteroalkyl, and heteroaryl is optionally substituted with one or more R^{12} independently

46. Hemisuccinate salt according to any one of the claims 1 to 45 wherein R^{12} is H, C_1-C_{10} alkyl, $-CF_3$, cyano, halogen, -OH, -COMe, $-NH_2$, $-NO_2$

47. Hemisuccinate salt according to claim 46 wherein R^{12} is H, $-CF_3$, cyano, halogen, -OH, $-NH_2$

48. Hemisuccinate salt according to claim 47 wherein R^{12} is –OH or $-NH_2$

49. Hemisuccinate salt according to any one of the claims 1 to 48 wherein n is two.

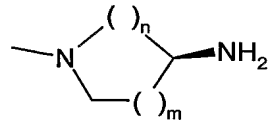
50. Hemisuccinate salt according to any one of the claims 1 to 48 wherein n is one.

51. Hemisuccinate salt according to any one of the claims 1 to 50 wherein m is two or three.

52. Hemisuccinate salt according to claim 51 wherein m is two

53. Hemisuccinate salt according to claim 51 wherein m is three

54. Hemisuccinate salt according to any one of the claims 1 to 53 wherein A is



55. Use of hemisuccinate salt according to any one of the claims 1 to 54 for the manufacture of a medicament for treatment of type 2 diabetes

56. A pharmaceutical composition for treatment or prevention of type 2 diabetes comprising hemisuccinate salt according to any of the claims 1 to 54, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents

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(54) Title: HETERO-SUBSTITUTED BENZIMIDAZOLE COMPOUNDS AND ANTIVIRAL USES THEREOF

(57) Abstract: The present invention relates to novel hetero-substituted benzimidazole compounds that have useful antiviral activity. More specifically, the invention encompasses hetero-substituted benzimidazole compounds that inhibit membrane fusion associated events such as viral transmission, reduce viral load or otherwise treat viral infections. The invention also encompasses the use of hetero-substituted benzimidazole compounds as inhibitors of membrane fusion associated events, such as viral transmission. In another embodiment, the invention encompasses processes for making hetero-substituted benzimidazole compounds, methods of using the hetero-substituted benzimidazole compounds and compositions comprising the hetero-substituted benzimidazole compounds. Finally, the invention provides methods for treating, preventing or ameliorating symptoms associated with respiratory infection, particularly that caused by Respiratory Syncytial Virus utilizing the novel benzimidazole compounds of the invention.

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HETERO-SUBSTITUTED BENZIMIDAZOLE COMPOUNDS AND ANTIVIRAL USES THEREOF

1. INTRODUCTION

[0001] The present invention relates to novel hetero-substituted benzimidazole compounds that have useful antiviral activity. More specifically, the invention encompasses hetero-substituted benzimidazole compounds that inhibit membrane fusion associated events such as viral transmission, reduce viral load or otherwise treat viral infections. The invention also encompasses the use of hetero-substituted benzimidazole compounds as inhibitors of membrane fusion associated events, such as viral transmission. In another embodiment, the invention encompasses processes for making hetero-substituted benzimidazole compounds, methods of using the hetero-substituted benzimidazole compounds and compositions comprising the hetero-substituted benzimidazole compounds. Finally, the invention provides methods for treating, preventing or ameliorating one or more symptoms associated with respiratory infection, particularly that caused by Respiratory Syncytial Virus utilizing the novel hetero-substituted benzimidazole compounds of the invention.

2. BACKGROUND OF THE INVENTION

[0002] Respiratory infections strike millions of people each year and collectively cause more deaths than any single infectious disease (National Institute of Allergy and Infectious Diseases News Release, October 30, 2000). Respiratory illness is most commonly caused by a viral infection.

[0003] Paramyxoviruses cause several respiratory diseases in humans and animals. Of these viruses, Respiratory Syncytial Virus ("RSV"), is an infectious agent that causes epidemics associated with extensive mortality and morbidity. The yearly epidemic nature of RSV infection is evident worldwide, but the incidence and severity of RSV disease in a given season vary by region (Hall, C.B., 1993, *Contemp. Pediatr.* 10:92-110). In temperate regions of the northern hemisphere, it usually begins in late fall and ends in late spring. Propagation of outbreaks is facilitated by the ease of transmission of RSV, which occurs by exposure to droplets of respiratory secretions of infected individuals (Hall *et al.*, 1981, *J. Pediatr.* 99:101-103).

[0004] RSV is the leading cause of serious lower respiratory tract disease in infants and children (Feigen *et al.*, eds., 1987, *In: Textbook of Pediatric Infectious Diseases*, WB Saunders, Philadelphia at pages 1653-1675; *New Vaccine Development, Establishing*

Priorities, Vol. 1, 1985, National Academy Press, Washington DC at pages 397-409; and Ruuskanen *et al.*, 1993, *Curr. Probl. Pediatr.* 23:50-79). By the age of three, virtually every child in America has had at least one respiratory infection caused by RSV. Of the eight million children under the age of five infected by RSV in the United States each year, approximately 5,000 die, another 100,000 are hospitalized, and 2.4 million are treated by a physician. Primary RSV infection occurs most often in children from 6 weeks to 2 years of age and uncommonly in the first 4 weeks of life during nosocomial epidemics (Hall *et al.*, 1979, *New Engl. J. Med.* 300:393-396). Children at increased risk from RSV infection include preterm infants (Hall *et al.*, 1979, *New Engl. J. Med.* 300:393-396) and children with bronchopulmonary dysplasia (Groothuis *et al.*, 1988, *Pediatrics* 82:199-203), congenital heart disease (MacDonald *et al.*, *New Engl. J. Med.* 307:397-400), congenital or acquired immunodeficiency (Ogra *et al.*, 1988, *Pediatr. Infect. Dis. J.* 7:246-249; and Pohl *et al.*, 1992, *J. Infect. Dis.* 165:166-169), and cystic fibrosis (Abman *et al.*, 1988, *J. Pediatr.* 113:826-830). The fatality rate in infants with heart or lung disease who are hospitalized with RSV infection is 3%-4% (Navas *et al.*, 1992, *J. Pediatr.* 121:348-354).

[0005] RSV infects adults as well as infants and children. In healthy adults, RSV causes predominantly upper respiratory tract disease. Several epidemics have been reported among nursing home patients and institutionalized young adults (Falsey, 1991, *Infect. Control Hosp. Epidemiol.* 12:602-608; and Garvie *et al.*, 1980, *Br. Med. J.* 281:1253-1254). RSV may cause serious disease in immunosuppressed persons, particularly bone marrow transplant patients (Hertz *et al.*, 1989, *Medicine* 68:269-281). RSV has also been reported as a problem in individuals undergoing cardiac, renal and lung transplants and in leukemia patients (Sinnot, *et al.*, 1988, *J. Infect. Dis.* 158:650-651; Peigue-Lafeuille *et al.*, 1990, *Scand. J. Infect. Dis.* 22:87-89; Doud *et al.*, 1992, *J. Heart Lung Transplant* 11:77-79; and Whimbey *et al.*, *Clin. Infect. Dis.* 21:376-379).

[0006] RSV is a non-segmented, negative-stranded RNA virus of the Paramyxoviridae family. RSV replicates in the cytoplasm of infected host cells and buds through the apical membrane, thereby acquiring its lipid envelope. The entire genetic material is associated with virus-encoded proteins, including the polymerase, which together form the nucleocapsid and are packaged in the virion (Collins *et al.*, 1996, *In: Virology*, Raven Press at pp. 1313-1351). The 15,222 nucleotide genome encodes ten major proteins of which three, the F (fusion), G (attachment) and small hydrophobic SH (unknown function) proteins, are expressed on the virion surface and anchored in the lipid membrane (Collins *et al.*, 1984, *J. Virol.* 49:572-578). Of the surface proteins, the F protein has emerged as a target for therapeutic intervention, largely in part because of its crucial role in

viral entry. The F protein is thought to mediate fusion of virus and host cell membranes in a fashion that is common to many viruses; however, the mechanism of RSV viral fusion remains to be determined. Although antiviral strategy targeting the fusion pathway of viruses such as HIV has been successful, a need for successful antiviral strategies against RSV still exists.

[0007] Treatment options for established RSV disease are limited. Severe RSV disease of the lower respiratory tract requires considerable supportive care, including administration of humidified oxygen and respiratory assistance (Fields *et al.*, eds., 1990, *Fields Virology*, 2nd ed., Vol. 1, Raven Press, New York at pages 1045-1072). Understanding of molecular aspects of the RSV life cycle is limited and has prevented a more fundamental, mechanism-based approach for antiviral drug discovery. As a consequence, most inhibitors of RSV disclosed to date have been discovered by a strategy of screening using a tissue cell culture assay.

[0008] The only clinically approved small-molecule therapy for the treatment of RSV infection is the antiviral agent ribavirin (marketed for RSV by ICN Pharmaceuticals, Costa Mesa, CA) (American Academy of Pediatrics Committee on Infectious Diseases, 1993, *Pediatrics* 92:501-504). Ribavirin is a nucleoside analog, but the precise mode of action remains to be established (Patterson *et al.*, 1997, *Rev. Infect. Dis.* 12:1139-1146). The compound is effective *in vitro* against a broad spectrum of RNA viruses, and the inhibition of influenza virus by ribavirin is well-studied. This compound has been shown to be effective in the treatment of RSV pneumonia and bronchiolitis and has been shown to modify the course of severe RSV disease in immunocompetent children (Smith *et al.*, 1991, *New Engl. J. Med.* 325:24-29). However, ribavirin has had limited use against RSV infection because it requires prolonged aerosol administration and because of concerns about its potential risks and side effects.

[0009] In addition to nucleoside analogs, several other agents have been investigated as anti-RSV molecules. Some agents have been characterized as inhibitors of RSV adsorption, although a detailed understanding of their mode of action remains to be elucidated. Examples of such agents are peptidic fusion inhibitors based on the identification of domains in the RSV F protein hypothesized to interact with each during stages of the fusion process. Because of the difficulties associated with identifying inhibitors of viral proteins and a limited range of targets, viruses such as RSV have also emerged as candidates for the development of therapeutics based on antisense oligonucleotides.

[0010] The difficulties in finding effective therapeutic agents has led to a focus on finding agents for the prevention of RSV infection. No vaccine is yet licensed for this indication. A major obstacle to vaccine development is safety. Several candidate RSV vaccines have been abandoned and others are under development (Murphy *et al.*, 1994, *Virus Res.* 32:13-36), but even if safety issues are resolved, vaccine efficacy must also be improved. Recently, antibodies designed to induce passive immunization, such as Synagis® (a monoclonal antibody developed by MedImmune, Gaithersburg, MD), have proved to be safer and more efficient than viral vaccines (Hemming *et al.*, 1995, *Clin. Microb. Rev.* 8:22-33; Weltzin, 1998, *Expert Opin. Invest. Drugs* 7:1271-1283). However, even though the characterization of prophylactic agents has yielded promising results, effective therapeutic agents are still needed for the treatment of established RSV infection. Primary RSV infection and disease do not protect well against subsequent RSV disease (Henderson *et al.*, 1979, *New Engl. J. Med.* 300:530-534).

[0011] Although many agents are being investigated, potent and specific, orally active antiviral agents have yet to be definitively characterized. So far, there is no ideal treatment for RSV infection, and there is no cure. Accordingly, novel therapeutics are needed that more effectively treat RSV infection. In particular, compounds for the treatment or prevention of RSV infection as a primary or secondary infection in patients as described above is contemplated herein.

[0012] In addition, RSV infection is often mistaken for human parainfluenza virus ("HPIV") and influenza virus infection. (Collins *et al.*, 1996, *Virology* pp.1313-1351, Raven Press). HPIVs are also paramyxoviruses and are a common cause of lower respiratory tract disease in young children and can also cause serious lower respiratory tract disease with repeat infection (*e.g.*, pneumonia, bronchitis, and bronchiolitis) among the elderly and those with compromised immune systems. HPIVs are spread from respiratory secretions through close contact with infected persons or contact with contaminated surfaces or objects. Human metapenumovirus ("hMPV") is an infectious respiratory paramyxovirus which is believed to be a common cause of serious lower respiratory tract infections particularly in young chiuldren. (Stockton *et. al. Emerg. Infect. Dis.* 2002 8 (9): 897-901). Influenza viruses are divided into three types, designated A, B, and C.Influenza types A and B are responsible for epidemics of respiratory illness that occur almost every winter and are often associated with increased rates for hospitalization and death. Influenza type C differs from types A and B in some important ways. Type C infection usually causes either a very mild respiratory illness or no symptoms at all; it does not cause epidemics and does not have the severe public health impact that influenza types A and B do. Accordingly, novel

therapeutics for the nonspecific treatment or prevention of respiratory illnesses caused by viral infection are also contemplated herein.

2.1 Benzimidazole Compounds

[0013] Specific benzimidazole compounds have been tested for antiviral activity. For example 2-(α-hydroxybenzyl)benzimidazole inhibits poliovirus type 1 in monkey kidney and HeLa cell cultures. A.C. Hollinshead *et al.*, *J. Pharmacol. Exp. Ther.*, **1958**, *123*, 54. (For purposes of discussion, the benzimidazoles are numbered using the system illustrated in Figure 1.) However, large concentrations of the specific benzimidazole was required to obtain any activity. *Id.* Other benzimidazole compounds directed to the hepatitis B virus were designed as nucleoside analogs, *i.e.*, the benzimidazoles were produced containing a carbocyclic ring in place of the sugar residue. *See* United States patent No. 5,399,580. Accordingly, these compounds were substituted only with 5-membered rings at the 1 position of the benzimidazole ring. *Id.*

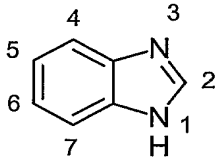


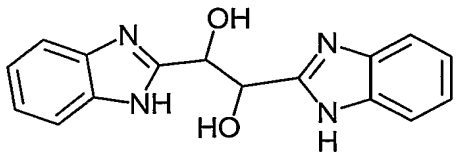
Figure 1

[0014] Eli Lilly and Company studied substituted benzimidazole compounds with antiviral activity, however, activity was only shown for compounds having a benzophenone like structures, *i.e.*, benzimidazoles with a carbonylbenzyl functional group at the 6 position. *See* United States patent No. 5,545,653. Although tested against poliovirus, rhinovirus, and coxsackie virus, toxic concentration levels were not determined, *i.e.*, the cytotoxicity of the compounds was never studied to determine the safety of the compounds. These limited benzophenone like compounds were further studied by replacing the carbonyl functionality for acetylene and substituted acetylenes. *See* WO 96/40125. Activity, however, was shown only for acetylene substituted benzophenones that also required either a phenyl or thiazole ring at the 1 position of the benzimidazoles. *Id.*

[0015] In attempts to further enhance antiviral activity, others substituted benzimidazoles at the 2 position, however, these compounds were limited to benzotriazole substituted benzimidazoles. *See* WO 00/04900.

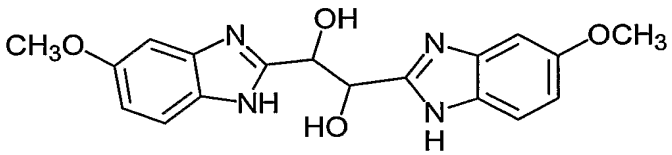
[0016] Compounds with a benzimidazole ring substituted at the 2-position of a benzimidazole ring have been studied for antiviral activity and it appears that these are the first class of compounds reported to inhibit all known serotypes of rhinovirus in cell culture. J.B. Scheleicher, *et al.*, *Applied Microbiology*, **1972**, *23*, 113-116. However, success was

dampened by the fact that not all compounds were active. Thus, there has yet to be developed a predictable structure-activity relationship with such 2-substituted compounds. *Id.* In particular, benzimidazole, 2-(α-hydroxybenzyl)benzimidazole, and 1,2-bis(2-benzimidazole)-1,2-ethanediol have been reported to be active antiviral agents against an assortment of picornaviruses. *Id.* However, there is considerable variation in the susceptibility of picornaviruses to any single antiviral compound and high concentrations were required to obtain any activity. *Id.*



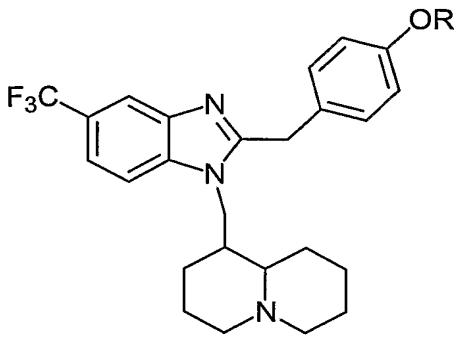
1,2-bis(2-benzimidazole)-1,2-ethanediol

[0017] Reportedly, compounds with two benzimidazole rings substituted at the 5-position are active against plaques of poliovirus type 1. W.R. Roderick, *et al.*, "Bisbenzimidazoles. Potent Inhibitors of Rhinoviruses," *J. Med. Chem.*, **1972**, *15*, 655-658. In particular, 5-methoxybenzimidazole has been found to be a potent inhibitor of rhinoviruses producing 100% inhibition of the cytopathic effect. *Id.* Substitution at the 5-position, however, does not guarantee effectiveness, as demonstrated by the lack of activity of the 5-chloro substituted benzimidazole. *Id.* Also, monobenzimidazoles with similar substitution patterns do not inhibit rhinoviruses, although some have been reported to inhibit poliovirus. *Id.* Accordingly, predicting the activity of benzimidazoles is complex and does not follow any established pattern. *Id.*



1,2-(5-methoxy-2-benzimidazole)-1,2-ethanediol

[0018] 2-Benzyl-benzimidazole compounds substituted with alkyl amine groups at the 1 position allegedly posses anti-inflammatory and anti-pyretic properties. *See* United States patent No. 3,394,141. However, these compounds have not shown any antiviral activity.

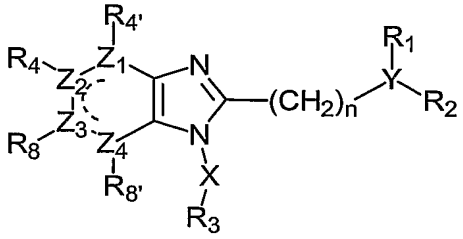


2-Benzyl-benzimidazole

[0019] Although some benzimidazole compounds posses antiviral activity, structure reactivity predictability is unknown. More importantly, benzimidazole compounds having a second benzimidazole ring at the 2 position have shown variable antiviral activity; thus, it appears that studies did not progress to include toxicity. Clearly, there is a great need for potent and non-toxic antiviral compounds, particularly, anti-RSV compounds. The hetero-substituted benzimidazole compounds of the present invention have enhanced antiviral activity with low cytotoxicity, and they are readily synthesized from standard starting materials.

3. SUMMARY OF THE INVENTION

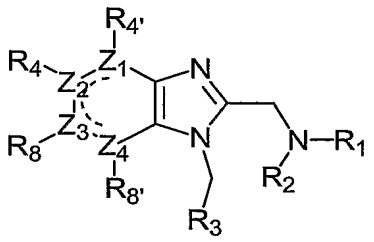
[0020] The invention encompasses the discovery of a novel class of hetero-substituted benzimidazoles that are potent and selective antivirals. In particular, the compounds of the invention are selective for virally infected cells and thus have little or no cytotoxicity for healthy or uninfected cells. In preferred embodiments, the hetero-substituted benzimidazole compounds demonstrate high inhibitory activity against viruses and low cytotoxicity activity against host cells. Such compounds are particularly useful *in vivo* for the treatment or prevention of viral-mediated diseases or infections. Accordingly, the present invention relates to hetero-substituted benzimidazole compounds which have utility in the treatment, prevention or amelioration of one or more symptoms associated with a viral infection. In particular, the invention encompasses hetero-substituted benzimidazole compounds which have utility in the treatment, prevention or amelioration of one or more symptoms associated with RSV infection. Additionally, the invention encompasses hetero-substituted benzimidazole compounds which have utility in the inhibition or downregulation of HPIV, hMPV or influenza virus replication. The hetero-substituted benzimidazole compounds of the present invention are compounds of the formula:



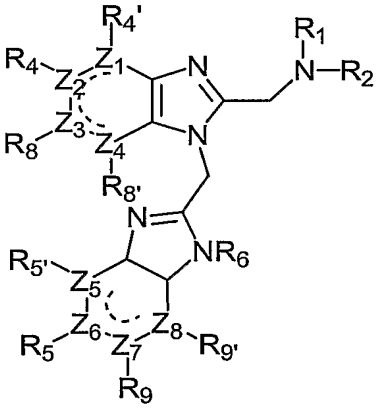
Formula I

described below in detail.

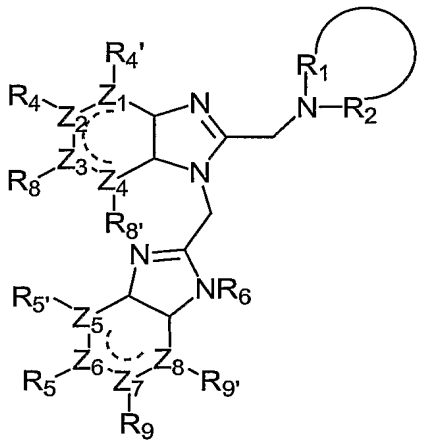
[0021] The compounds of the invention also encompass compounds of the following formulas:



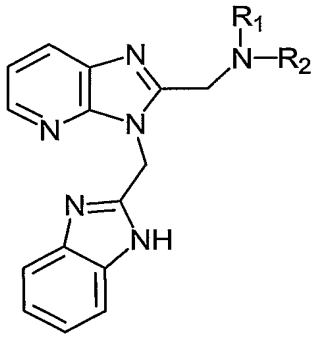
Formula II



Formula III

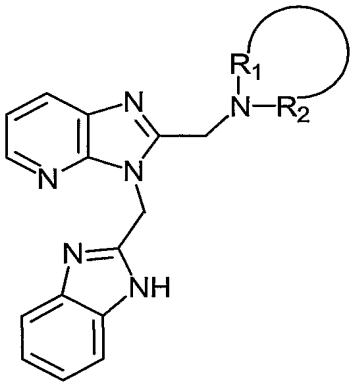


Formula IV



Formula V

or



Formula VI

wherein R_1, R_2, R_3, R_4, $R_{4'}$, R_5, $R_{5'}$, R_6, R_7, $R_{7'}$, R_8, $R_{8'}$, R_9, $R_{9'}$, X, Y, Z_1, Z_2, Z_3, Z_4, Z_5, Z_6, Z_7, Z_8, m and n are as defined below. Preferred embodiments are set forth below.

[0022] The present invention is based in part on novel hetero-substituted benzimidazole compounds which have a utility for treating, preventing or ameliorating one or more symptoms associated with viral infection, such as RSV infection, HPIV infection and hMPV infection. Although not intending to be bound by any mechanism of action, the hetero-substituted benzimidazole compounds are predicted to inhibit or interfere with viral membrane fusion associated events.

[0023] In certain embodiments, the invention encompasses methods for treating, preventing or ameliorating one or more symptoms associated with a viral infection in a subject comprising administering to said subject one or more hetero-substituted benzimidazole compounds of the invention. In another embodiment, the invention includes the treatment of viral infection by the inhibition of membrane fusion associated events. In other embodiments, the invention includes: (a) methods of inhibiting viral transmission from cell to cell and/or replication; and (b) methods of reducing viral titer and viral load.

[0024] The invention also encompasses methods for treating, preventing or ameliorating one or more symptoms associated with RSV infection in a subject comprising administering to said subject one or more hetero-substituted benzimidazole compounds of

the invention. In a preferred embodiment, the hetero-substituted benzimidazole is substituted in the 1-position by a methylene-benzimidazole moiety. In another preferred embodiment, the hetero-substituted benzimidazole is substituted in the R_4 or R_8 position of formulas I, II, III, and IV.

[0025] The present invention also provides pharmaceutical compositions comprising one or more hetero-substituted benzimidazole compounds of the invention, including single unit dosage forms for oral administration, parenteral administration, intranasal administration, and by aerosol or other means directly into the lung. Thus, both solid and liquid formulations are encompassed as well as sterile compositions. Lyophilized powders suitable for reconstitution are also contemplated by the invention.

[0026] Also encompassed by the invention are methods of delivering one or more hetero-substituted benzimidazole compounds, kits comprising one or more hetero-substituted benzimidazole compounds or kits comprising one or more pharmaceutical compositions comprising one or more hetero-substituted benzimidazole compounds, as well as therapeutic protocols comprising the administration of one or more hetero-substituted benzimidazole compounds in combination with other prophylactic or therapeutic agents such as but not limited to antiviral, anti-inflammatory, anti-parasitic, anti-cancer and antibiotic agents.

3.1 Definitions

[0027] As used herein, the terms used have the following meaning:

[0028] As used herein, the term "hetero-substituted benzimidazole" means a benzimidazole moiety containing a heteroatom, independently selected from nitrogen, oxygen, or sulfur, at least one of the 4, 5, 6, or 7 positions.

[0029] As used herein, unless otherwise specified the term "alkyl" means a straight chain or branched saturated hydrocarbon moiety. An alkyl group can be unsubstituted or substituted. Unsaturated alkyl groups include alkenyl groups and alkynyl groups, which are discussed below.

[0030] As used herein, unless otherwise specified the term "alkenyl group" means a monovalent unbranched or branched hydrocarbon chain having one or more double bonds therein. The double bond of an alkenyl group can be unconjugated or conjugated to another unsaturated group. An alkenyl group can be unsubstituted or substituted.

[0031] As used herein, unless otherwise specified the term "alkynyl group" means a monovalent unbranched or branched hydrocarbon chain having at least one triple bond therein. The triple bond of an alkynyl group can be unconjugated or conjugated to another unsaturated group. An alkynyl group can be unsubstituted or substituted.

[0032] As used herein, unless otherwise specified the term "halogen" means fluorine, chlorine, bromine, or iodine.

[0033] As used herein, unless otherwise specified the term "alkyl sulfonyl" means -Alkyl-SO_3H or -SO_3-alkyl, wherein alkyl is defined as above.

[0034] As used herein, unless otherwise specified the term "carboxyl" means -COOH.

[0035] As used herein, unless otherwise specified the term "alkoxy" means -O-(alkyl), wherein alkyl is defined above.

[0036] As used herein, unless otherwise specified the term "alkoxycarbonyl" means -C(=O)O-(alkyl), wherein alkyl is defined above.

[0037] As used herein, unless otherwise specified the term "alkoxy alkyl" means -(alkyl)-O-(alkyl), wherein each "alkyl" is independently an alkyl group as defined above.

[0038] As used herein, unless otherwise specified the term "aryl" means a carbocyclic aromatic ring containing from 5 to 14 ring atoms. The ring atoms of a carbocyclic aryl group are all carbon atoms, such as, phenyl, tolyl, anthracenyl, fluorenyl, indenyl, azulenyl, and naphthyl, as well as benzo-fused carbocyclic moieties such as 5,6,7,8-tetrahydronaphthyl and the like. A carbocyclic aryl group can be unsubstituted or substituted.

[0039] As used herein, unless otherwise specified the term "heteroaryl" means a carbocyclic aromatic ring containing from 5 to 14 ring atoms and the ring atoms contain at least one heteroatom, preferably 1 to 3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur. Heteroaryl ring structures include compounds having one or more ring structures such as mono-, bi-, or trycylic compounds. Illustrative examples of heteroaryl groups are pyridinyl, pyridazinyl, pyrimidyl, pyrazyl, benzimidazolyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3,)- and (1,2,4)-triazolyl, pyrazinyl, pyrimidinyl, tetrazolyl, furyl, thienyl, isothiazolyl, thiazolyl, furyl, phienyl, isoxazolyl, oxadiazolyl, and oxazolyl. A heteroaryl group can be unsubstituted or substituted.

[0040] As used herein, unless otherwise specified the term "aryloxy" means –O–aryl group, wherein aryl is as defined above. An aryloxy group can be unsubstituted or substituted.

[0041] As used herein, unless otherwise specified the term"arylalkyl" means -(alkyl)-(aryl), wherein alkyl and aryl are defined above.

[0042] As used herein, unless otherwise specified the term "arylalkyloxy" means -O-(alkyl)-(aryl), wherein alkyl and aryl are defined above.

[0043] As used herein, unless otherwise specified the term "cycloalkyl" means a monocyclic or polycyclic saturated ring comprising carbon and hydrogen atoms and having no carbon-carbon multiple bonds. A cycloalkyl group can be unsubstituted or substituted. Preferably, the cycloalkyl group is a monocyclic ring or bicyclic ring.

[0044] As used herein, unless otherwise specified the term "heterocyclyl" means a monocyclic or polycyclic ring comprising carbon and hydrogen atoms, optionally having 1 or 2 multiple bonds, and the ring atoms contain at least one heteroatom, preferably 1 to 3 heteroatoms, independently selected from nitrogen, oxygen, and sulfur. Heterocyclyl ring structures include compounds having one or more ring structures such as mono-, bi-, or trycylic compounds. Preferably, the heterocyclyl group is a monocyclic ring or bicyclic ring. Illustrative examples include, but are not limited to, oxiranyl, 2H-pyranyl, 4H-pyranyl, parathiazinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, and morpholinyl. A heterocyclyl ring can be unsubstituted or substituted.

[0045] As used herein, unless otherwise specified the term "cycloalkyloxy" means -O-(cycloalkyl), wherein cycloalkyl is defined above.

[0046] As used herein, unless otherwise specified the term "cycloalkylalkyloxy" means -O-(alkyl)-(cycloalkyl), wherein cycloalkyl and alkyl are defined above.

[0047] As used herein, unless otherwise specified the term "aminoalkoxy" means -O-(alkyl)-NH_2, wherein alkyl is defined above.

[0048] As used herein, unless otherwise specified the term "alkylamino" means -NH(alkyl) or -N(alkyl)(alkyl), wherein alkyl is defined above.

[0049] As used herein, unless otherwise specified the term "arylamino" means -NH(aryl), wherein aryl is defined above.

[0050] As used herein, unless otherwise specified the term "arylalkylamino" means -NH-(alkyl)-(aryl), wherein alkyl and aryl are defined above.

[0051] As used herein, unless otherwise specified the term "cycloalkylamino" means -NH-(cycloalkyl), wherein cycloalkyl is defined above.

[0052] As used herein, unless otherwise specified the term "aminoalkyl" means -(alkyl)-NH_2, wherein alkyl is defined above.

[0053] As used herein, unless otherwise specified the term "alkylaminoalkyl" means -(alkyl)-NH(alkyl) or -(alkyl)-N(alkyl)(alkyl), wherein each "alkyl" is independently an alkyl group defined above.

[0054] As used herein, the term "pharmaceutically acceptable salts" refer to salts of compounds of Formula I-VI. prepared from pharmaceutically acceptable non- toxic acids or bases including inorganic acids and bases and organic acids and bases. Suitable

pharmaceutically acceptable base addition salts for the compound of the present invention include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Suitable non-toxic acids include, but are not limited to, inorganic and organic acids such as acetic, alginic, anthranilic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, formic, fumaric, furoic, galacturonic, gluconic, glucuronic, glutamic, glycolic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phenylacetic, phosphoric, propionic, salicylic, stearic, succinic, sulfanilic, sulfuric, tartaric acid, and p-toluenesulfonic acid. Specific non-toxic acids include hydrochloric, hydrobromic, phosphoric, sulfuric, and methanesulfonic acids. Examples of specific salts thus include xinofoate, hydrochloride mesylate, zinc, potassium, or iron salts. In certain embodiments, both water-soluble and water-insoluble salts will be useful based on the mode of administration. Thus, the term "pharmaceutically acceptable salt(s)" of a compound of Formula I-VI is intended to encompass any and all acceptable salt forms.

[0055] As used herein and unless otherwise indicated, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide the compound. Examples of prodrugs include, but are not limited to, derivatives and metabolites of Compound A that include biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Prodrugs can typically be prepared using well-known methods, such as those described by 1 *Burger's Medicinal Chemistry and Drug Discovery*, 172-178, 949-982 (Manfred E. Wolff ed., 5th ed. 1995).

[0056] As used herein and unless otherwise indicated, the terms "biohydrolyzable amide," "biohydrolyzable ester," "biohydrolyzable carbamate," "biohydrolyzable carbonate," "biohydrolyzable ureide," "biohydrolyzable phosphate" mean an amide, ester, carbamate, carbonate, ureide, or phosphate, respectively, of a compound that either: 1) does not interfere with the biological activity of the compound but can confer upon that compound advantageous properties in vivo, such as uptake, duration of action, or onset of action; or 2) is biologically inactive but is converted in vivo to the biologically active compound. Examples of biohydrolyzable esters include, but are not limited to, lower alkyl esters, alkoxyacyloxy esters, alkyl acylamino alkyl esters, and choline esters. Examples of biohydrolyzable amides include, but are not limited to, lower alkyl amides, α-amino acid

amides, alkoxyacyl amides, and alkylaminoalkylcarbonyl amides. Examples of biohydrolyzable carbamates include, but are not limited to, lower alkylamines, substituted ethylenediamines, aminoacids, hydroxyalkylamines, heterocyclic and heteroaromatic amines, and polyether amines.

[0057] The term "human infant" as used herein refers to a human less than 24 months, preferably less than 16 months, less than 12 months, less than 6 months, less than 3 months, less than 2 months, or less than 1 month of age.

[0058] The term "human infant born prematurely" as used herein refers to a human born at less than 40 weeks gestational age, preferably less than 35 weeks gestational age, who is less than 6 months old, preferably less than 3 months old, more preferably less than 2 months old and most preferably less than 1 month old.

[0059] As used herein, unless otherwise specified, a "therapeutically effective amount" refers to that amount of the compound sufficient to result in amelioration of one or more symptoms of a disease. The term is also meant to include the amount of the compound sufficient to result in inhibition of or interference with membrane fusion events, viral entry, viral replication or viral infection. The term also encompasses the inhibition of viral transmission or prevention of viral establishment in its host. One such measure is reduction in viral load or viral pathogenesis or decrease in mortality and/or morbidity.

[0060] As used herein, unless otherwise specified, a "prophylactically effective amount" refers to that amount of the compound sufficient to result in the prevention of the onset or recurrence of symptoms of an infection. The term is also meant to include the amount of the compound sufficient to result in the prevention of one or more of membrane fusion events, viral entry, viral replication or viral infection. The term also encompasses the prevention of viral transmission or viral establishment in its host.

[0061] As used herein, unless otherwise specified, "inhibition of membrane fusion associated events", "anti-membrane fusion capability" and "antifusogenic" refer to the ability to block, reduce or prevent one or more of the occurrence of viral fusion with a host cell, or viral binding and/or attachment to a host cell receptor. The terms also refer to a compound's ability to inhibit or reduce the level of membrane fusion events between two or more moieties relative to the level of membrane fusion which occurs between said moieties in the absence of the compound. The moieties may be, for example, cell membranes or viral structures. Also encompassed by the terms are the ability of a compound to interfere with or inhibit viral entry into its host cell.

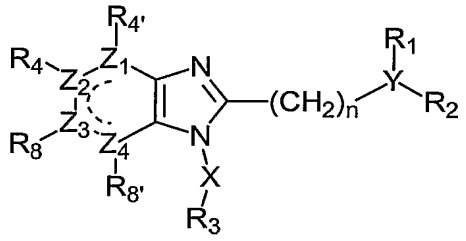
[0062] As used herein, unless otherwise specified, the term "antiviral activity" is meant to include partial and total inhibition of viral replication as well as decreases in the

rate of viral replication. The term antiviral activity can also refer to any activity that results in the reduced function, activity or expression of a virus. Antiviral activity also refers to the prevention by down-regulation or inhibition of a protein required in the viral fusion pathway or the viral replication pathway or by interference with membrane fusion associated events. A compound with antiviral activity can interfere with or inactivate or destroy viral replication or infectivity. Accordingly, the term includes references to the compound's ability to inhibit viral infection of cells, via, for example, cell-cell fusion or free virus infection. Such infection may involve membrane fusion, as occurs in the case of enveloped viruses, or some other fusion event involving a viral structure and a cellular structure (*e.g.*, such as the fusion of a viral pilus and bacterial membrane during bacterial conjugation). A compound with antiviral activity can also interfere with or inhibit or prevent viral entry into a host, viral transmission to a host, or viral establishment in its host. One skilled in the art could readily measure antiviral activity by a reduction in viral load or viral pathogenesis or decrease in mortality and/or morbidity.

4. DETAILED DESCRIPTION OF THE INVENTION

4.1 Hetero-substituted Benzimidazole Compounds

[0063] The present invention encompasses hetero-substituted benzimidazole compounds, preferably, di-substituted hetero-substituted benzimidazole compounds substituted at the 1- and 2- positions, preferably via an alkyl, or more preferably substituted with a methylene-hetero-substituted benzimidazole. The compounds of the invention encompass compounds with antiviral activity and low cytotoxicity. In one embodiment, the present invention encompasses compounds of the general Formula I:



Formula I

or a pharmaceutically-acceptable prodrug, salt, solvate including hydrate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof, wherein:

[0064] Z_1, Z_2, Z_3 and Z_4 are each independently nitrogen or carbon and at least one of Z_1, Z_2, Z_3 and Z_4 is carbon;

[0065] preferably one of Z_2 and Z_4 is nitrogen; more preferably Z_2 and Z_4 are both nitrogen and most preferably only Z_4 is nitrogen;

[0066] R_1 and R_2 are each independently: hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted arylalkyl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, thioaryl, or R_1 and R_2 may be joined to form a substituted or unsubstituted ring including a heterocycloalkyl, heterocycloaryl or heteroaryl group;

[0067] preferably, R_1 and R_2 are each independently C_1-C_8 saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted 4 to 12 membered heterocycloalkyl or heteroaryl group having at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is least one C_1-C_4 alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, ester, amine, or C_1-C_4 alkylamine;

[0068] more preferably, R_1 and R_2 are each independently C_1-C_4 saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 5 to 8 membered aryl, substituted or unsubstituted 5 to 8 membered arylalkyl, or substituted or unsubstituted 4 to 9 membered heterocycloalkyl or heteroaryl with at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is least one C_1-C_4 alkyl, hydroxy, fluoride, chloride, bromide, methoxy, ethoxy, carboxylic acid, ester, amine, or C_1-C_4 alkylamine; and

[0069] most preferably, R_1 and R_2 are each independently benzyl, cyclopentyl, cyclohexyl, isopropyl, propyl, butyl, methylene cyclopropyl, methylene cyclobutyl, benzimidazolyl, methylene benzimidazolyl, or R_1 and R_2 are attached to form a pyrrolidinyl or piperidinyl ring.

[0070] R_3 is hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted

or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl; wherein, if present the substiuent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl;

[0071] preferably, R_3 is hydrogen, straight chain or branched substituted or unsubstituted C_1-C_8 alkyl or unsaturated alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted 4 to 12 membered heterocycloalkyl or heteroaryl having at least one oxygen, sulfur, or nitrogen atom within the ring, wherein the substituent is at least one hydroxy, fluoride, chloride, bromine, C_1-C_4 alkoxy, C_1-C_4 sulfide, C_1-C_4 sulfonyl, nitro, carboxylic acid, ester, amine, or C_1-C_4 alkylamine;

[0072] more preferably, R_3 is a substituted or unsubstituted C_1-C_4 straight chain or branched alkyl or unsaturated alkyl, substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 5 to 12 membered aryl, substituted or unsubstituted 6 to 12 membered arylalkyl, substituted or unsubstituted 4 to 12 membered heterocycloalkyl or heteroaryl with at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is at least one hydroxy, fluoride, chloride, bromide, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 sulfide, C_1-C_4 sulfonyl, nitro, carboxylic acid, ester, amine, or C_1-C_4 alkylamine; and

[0073] most preferably, R_3 is a substituted or unsubstituted phenyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted quinolinyl, substituted or unsubstituted acridinyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted benzimidazolyl, substituted or unsubstituted benzodioxanyl, substituted or unsubstituted phenylphenolyl, wherein, if present, the substituent is at least one C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 sulfide, C_1-C_4 sulfonyl, nitro, fluoride, chloride, or bromide.

[0074] R_4, $R_{4'}$, R_8, and $R_{8'}$ are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or

unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl; wherein, if present the substituent is at least one alkanoyl, imide, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl;

[0075] preferably, R_4, $R_{4'}$, R_8, and $R_{8'}$ are each independently hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, amine, C_1-C_4 alkylamine, carboxylic acid, ester, C_1-C_4 amide, halide, hydroxy, nitro, C_1-C_4 sulfide, C_1-C_4 sulfonyl, or sulfonamide;

[0076] more preferably, R_4 and R_8 are each independently hydrogen, C_1-C_2 alkyl, C_1-C_2 alkoxy, amine, C_1-C_2 alkylamine, fluoride, chloride, bromide, hydroxy, nitro, C_1-C_2 sulfide, or C_1-C_2 sulfonyl;

[0077] more preferably, $R_{4'}$ and $R_{8'}$ are each independently, hydrogen, C_1-C_2 alkyl, amine, C_1-C_2 alkylamine, C_1-C_2 alkoxy, carboxylic acid, C_2-C_4 ester, C_1-C_2 amide, or sulfonamide;

[0078] most preferably, R_4 and R_8 are each independently hydrogen, methyl, methoxy, thiomethyl, fluoride, chloride, nitro, or methylsulfonyl; and

[0079] most preferably, $R_{4'}$ and $R_{8'}$ are each independently, hydrogen, methyl, methyl ester, ethyl ester, C_1-C_2 amide, carboxylic acid, methoxy, or sulfonamide.

[0080] X is a bond, straight chain or branched substituted or unsubstituted alkyl or unsaturated alkyl, -(alkyl)N-, -(alkyl)O-, -C=N-, carbonyl, phosphorus, or sulfur;

[0081] preferably, X is a bond, straight chain or branched substituted or unsubstituted C_1-C_4 alkyl, -(C_1-C_4 alkyl)N-, -(C_1-C_4 alkyl)O-, carbonyl, or sulfur;

[0082] more preferably, X is a bond, methylene, ethylene, or carbonyl; and most preferably, X is methylene.

[0083] Y is nitrogen, phosphorus, oxygen, or sulfur; wherein, if Y is oxygen or sulfur, R_2 is not present; preferably Y is nitrogen, or phosphorus; and more preferably, Y is nitrogen.

[0084] The "n" is an integer from 0 to about 4; preferably n is from 0 to 1; and more preferably, n is 1.

[0085] In another embodiment of the compounds of Formula I, $R_{4'}$ and $R_{8'}$ are hydrogen. In another embodiment of the compounds of Formula I, R_4, $R_{4'}$, R_8, and $R_{8'}$ are all hydrogen. In yet another embodiment of the compounds of Formula I, at least one of R_4, $R_{4'}$, R_8, or $R_{8'}$ is not hydrogen. In yet another embodiment of the compounds of Formula I, at least two of R_4, $R_{4'}$, R_8, and $R_{8'}$ are not hydrogen. In another embodiment of the compounds of Formula I, at least three of R_4, $R_{4'}$, R_8, and $R_{8'}$ are not hydrogen.

[0086] With the proviso that compounds of Formula I do not include a compound where R_1, R_2, R_3, R_4, $R_{4'}$, R_8, $R_{8'}$ are hydrogen, X is a bond, and n = 0 or 1; or a compound where R_3, R_4, $R_{4'}$, R_8, and $R_{8'}$ are hydrogen, X is a bond, n = 0, one of R_1 or R_2 is a hydrogen, and the other is a 4-piperidinyl or N-substituted 4-piperidinyl.

[0087] Preferred compounds include, but are not limited to:

[0088] 3-(1H-Benzoimidazol-2-ylmethyl)-2-[4-(4-trifluoromethyl-phenyl)-piperazin-1-ylmethyl]-3H-imidazo[4,5-b]pyridine;

[0089] 3-(1H-Benzoimidazol-2-ylmethyl)-2-morpholin-4-ylmethyl-3H-imidazo[4,5-b]pyridine;

[0090] 2-[3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-1,2,3,4-tetrahydro-isoquinoline-6,7-diol;

[0091] 3-(1H-Benzoimidazol-2-ylmethyl)-2-piperazin-1-ylmethyl-3H-imidazo[4,5-b]pyridine;

[0092] 1-{4-[3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-piperazin-1-yl}-2-phenyl-ethanone;

[0093] 1-{4-[3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-piperazin-1-yl}-ethanone;

[0094] 3-(1H-Benzoimidazol-2-ylmethyl)-2-[4-(1-methyl-1H-imidazole-4-sulfonyl)-piperazin-1-ylmethyl]-3H-imidazo[4,5-b]pyridine;

[0095] 3-(1H-Benzoimidazol-2-ylmethyl)-2-[4-(thiophene-3-sulfonyl)-piperazin-1-ylmethyl]-3H-imidazo[4,5-b]pyridine;

[0096] 3-(1H-Benzoimidazol-2-ylmethyl)-2-[4-(2,4-difluoro-benzenesulfonyl)-piperazin-1-ylmethyl]-3H-imidazo[4,5-b]pyridine;

[0097] 3-(1H-Benzoimidazol-2-ylmethyl)-2-[4-(5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonyl)-piperazin-1-ylmethyl]-3H-imidazo[4,5-b]pyridine;

[0098] 3-(1H-Benzoimidazol-2-ylmethyl)-2-[4-(2,5-dimethyl-thiophene-3-sulfonyl)-piperazin-1-ylmethyl]-3H-imidazo[4,5-b]pyridine;

[0099] 4-[3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-piperazine-1-carboxylic acid (3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-amide;

[001] {1-[3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-pyrrolidin-2-yl}-methanol;

[002] 3-(1H-Benzoimidazol-2-ylmethyl)-2-[4-(4-trifluoromethyl-phenyl)-piperazin-1-ylmethyl]-3H-imidazo[4,5-b]pyridine;

[003] 2-[(2-{[3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-amino}-ethyl)-(2-hydroxy-ethyl)-amino]-ethanol;

[004] [3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-(2-morpholin-4-yl-ethyl)-amine;

[005] [3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-(2-methoxy-ethyl)-methyl-amine;

[006] [3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-(3-morpholin-4-yl-propyl)-amine;

[007] [3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-[3-(4-methyl-piperazin-1-yl)-propyl]-amine;

[008] 2-[(3-{[3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-amino}-propyl)-(2-hydroxy-ethyl)-amino]-ethanol;

[009] [3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-cyclopentyl-amine;

[010] 3-(1H-Benzoimidazol-2-ylmethyl)-2-(1,3-dihydro-isoindol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine;

[011] {1-[3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-pyrrolidin-2-yl}-methanol;

[012] [3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-benzyl-isopropyl-amine;

[013] 3-(1H-Benzoimidazol-2-ylmethyl)-2-[4-(4-trifluoromethyl-phenyl)-piperazin-1-ylmethyl]-3H-imidazo[4,5-b]pyridine;

[014] [3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-isopropyl-methyl-amine;

[015] 4-(2-{[3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-isopropyl-amino}-2-hydroxy-ethyl)-benzene-1,2-diol;

[016] {1-[3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-piperidin-3-yl}-methanol;

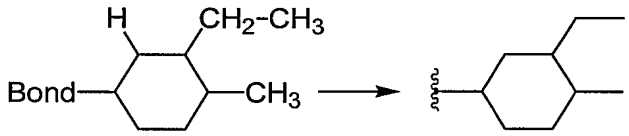
[017] [3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-(3-methoxy-propyl)-amine;

[018] 2-{1-[3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-piperidin-2-yl}-ethanol;

[019] {4-[3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-piperazin-1-yl}-furan-2-yl-methanone; and

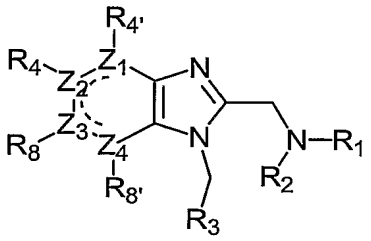
[020] [3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-diisopropyl-amine.

[021] A few examples of compounds of the invention are depicted in Tables 1 and 2 for illustration and not limitation. Because of possible discrepancies in using chemical nomenclature where structures are provided for compounds or moieties the structure controls the definition of the compound or moiety, if there is a discrepancy with the chemical name. Each compound in Table 1 has been prepared, isolated, purified, and tested for antiviral activity and cytotoxicity as discussed below. The drawings described below use standard chemical nomenclature. For example, terminal lines represent methyl groups and corners represent saturated carbons unless otherwise indicated:



A wavy line perpendicular to a terminal line represents a point of bond attachment.

[022] In another embodiment, the 2-position of the hetero-substituted benzimidazole ring is substituted with an aminoalkyl group, with reference to Formula I, X is methylene, Y is nitrogen, and n is 1, thus, in another embodiment, the present invention encompasses compounds of the general Formula II:



Formula II

or a pharmaceutically-acceptable prodrug, salt, solvate including hydrate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof, wherein:

[023] Z_1, Z_2, Z_3 and Z_4 are each independently nitrogen or carbon and at least one of Z_1, Z_2, Z_3 and Z_4 is carbon;

[024] preferably one of Z_2 and Z_4 is nitrogen; more preferably Z_2 and Z_4 are both nitrogen and most preferably only Z_4 is nitrogen;

[025] R_1 and R_2 are each independently: a straight or branched substituted or unsubstituted alkyl or unsaturated alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted arylalkyl, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, thioaryl, or R_1 and R_2 may be joined to form a ring including a heterocycloalkyl or heteroaryl group;

[026] preferably, R_1 and R_2 are each independently: C_1-C_8 straight chain or branched alkyl or substituted alkyl or unsaturated alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl,4 to 12 membered heterocycloalkyl or heteroaryl with at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is at least one hydroxy, halide, methoxy, ethoxy, carboxylic acid, ester, amine, or alkylamine;

[027] more preferably, R_1 and R_2 are each independently: C_1-C_4 straight chain or branched alkyl or unsaturated alkyl, substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 5 to 6 membered aryl, substituted or unsubstituted 5 to 8 membered arylalkyl, or 4 to 8 membered heterocycloalkyl or heteroaryl with at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is at least one hydroxy, fluoride, chloride, bromide, methoxy, ethoxy, carboxylic acid, ester, amine, or C_1-C_4 alkylamine; and

[028] most preferably, R_1 and R_2 are each independently: benzyl, cyclopentyl, cyclohexyl, isopropyl, propyl, butyl, methylene cyclopropyl, methylene cyclobutyl, or R_1 and R_2 are attached to form a pyrrolidinyl or piperidinyl ring.

[029] R_3 is hydrogen, halide, straight chained or branched substituted or unsubstituted alkyl or unsaturated alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl;

[030] preferably, R_3 is hydrogen, C_1-C_8 straight chain or branched substituted or unsubstituted alkyl or unsaturated alkyl, substituted or unsubstituted 3 to 8 membered

cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted 4 to 12 membered heterocycloalkyl or heteroaryl with at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is at least one hydroxy, halide, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 sulfide, C_1-C_4 sulfonyl, nitro, carboxylic acid, ester, amine, or C_1-C_4 alkylamine;

[031] more preferably, R_3 is C_1-C_4 straight chain or branched alkyl or unsaturated alkyl, substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 5 to 12 membered aryl, substituted or unsubstituted 5 to 12 membered arylalkyl, or 4 to 12 membered heterocycloalkyl or heteroaryl with at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is at least one hydroxy, halide, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 sulfide, C_1-C_4 sulfonyl, nitro, carboxylic acid, ester, amine, or C_1-C_4 alkylamine; and

[032] most preferably, R_3 is a substituted or unsubstituted phenyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted quinolinyl, substituted or unsubstituted acridinyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted benzodioxanyl, substituted or unsubstituted benzimidazolyl, substituted or unsubstituted phenylphenolyl, wherein, if present, the substituent is at least one C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 sulfide, C_1-C_4 sulfonyl, nitro, fluoride, chloride, bromide, or iodide.

[033] R_4, $R_{4'}$, R_8, and $R_{8'}$ are each independently hydrogen, halide, straight chained or branched substituted or unsubstituted alkyl or unsaturated alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl;

[034] preferably, R_4, $R_{4'}$, R_8, and $R_{8'}$ are each independently hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, amine, C_1-C_4 alkylamine, C_1-C_4 amide, carboxylic acid, ester, halide, hydroxy, nitro, C_1-C_4 sulfide, C_1-C_4 sulfonyl, or sulfonamide;

[035] more preferably, R_4 and R_8 are each independently are hydrogen C_1-C_2 alkyl, C_1-C_2 alkoxy, amine, C_1-C_2 alkylamine, fluoride, chloride, bromide, hydroxy, nitro, C_1-C_2 sulfide, or C_1-C_2 sulfonyl;

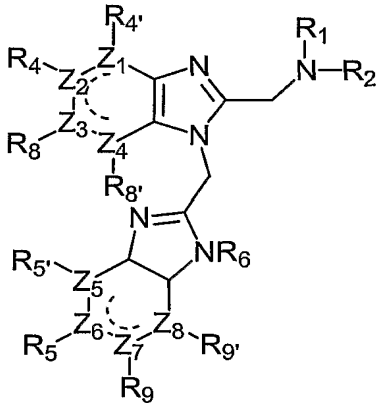
[036] more preferably, $R_{4'}$ and $R_{8'}$ are each independently, hydrogen, C_1-C_2 alkyl, amine, C_1-C_2 alkylamine, C_1-C_2 amide, carboxylic acid, C_2-C_4 ester, or sulfonamide;

[037] most preferably, R_4 and R_8 are each independently are hydrogen, methyl, methoxy, thiomethyl, fluorine, chlorine, nitro, or methylsulfonyl; and

[038] most preferably, $R_{4'}$ and $R_{8'}$ are each independently, hydrogen, methyl, methyl ester, ethyl ester, C_1-C_2 amide, carboxylic acid, methoxy, or sulfonamide.

[039] In another embodiment of the compounds of Formula II, $R_{4'}$ and $R_{8'}$ are hydrogen. In yet another embodiment of the compounds of Formula II, R_4, $R_{4'}$, R_8, and $R_{8'}$ are hydrogen. In yet another embodiment of the compounds of Formula II, at least one of R_4, $R_{4'}$, R_8, or $R_{8'}$ is not hydrogen. In another embodiment of the compounds of Formula II, at least two of R_4, $R_{4'}$, R_8, and $R_{8'}$ are not hydrogen. In another embodiment of the compounds of Formula II, at least three of R_4, $R_{4'}$, R_8, and $R_{8'}$ are not hydrogen.

[040] In a preferred embodiment of the invention, with reference to Formula II, R_3 is a substituted or unsubstituted hetero-substituted benzimidazole moiety, thus, the present invention encompasses compounds of the general Formula III:



Formula III

or a pharmaceutically-acceptable prodrug, salt, solvate including hydrate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof, wherein:

[041] Z_1, Z_2, Z_3 and Z_4 are each independently nitrogen or carbon and at least one of Z_1, Z_2, Z_3 and Z_4 is carbon;

[042] preferably one of Z_2 and Z_4 is nitrogen; more preferably Z_2 and Z_4 are both nitrogen and most preferably only Z_4 is nitrogen;

[043] Z_5, Z_6, Z_7 and Z_8 are each independently nitrogen or carbon;

[044] R_1 and R_2 are each independently: hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl, substituted or unsubstituted heteroaryl, alkanoyl, or imide, wherein, if present, the substituent is at least one alkyl, alkanoyl, imide, alkoxy, carboxylic acid, amine, alkylamine, cyano, halide, hydroxy, nitro, thiol, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl;

[045] preferably, R_1 and R_2 are each independently straight chain or branched substituted or unsubstituted C_1-C_{11} alkyl or unsaturated alkyl, C_1-C_{12} alkoxy, substituted or unsubstituted C_1-C_{11} alkylamino, substituted or unsubstituted 3 to 10 membered cycloalkyl, substituted or unsubstituted 3 to 10 membered heterocycloalkyl, substituted or unsubstituted 5 to 12 membered aryl, substituted or unsubstituted 5 to 12 membered arylalkyl, substituted or unsubstituted 4 to 13 membered heteroaryl, alkanoyl, or imide, wherein, if present, the substituent is at least one C_1-C_4 alkyl, cyano, fluoride, chloride, bromide, hydroxy, nitro, or thiol;

[046] more preferably, R_1 and R_2 are each independently straight chain or branched substituted or unsubstituted C_1-C_8 alkyl or unsaturated alkyl, C_1-C_4 alkoxy, substituted or unsubstituted C_2-C_6 alkylamino, substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 4 to 5 membered heterocycloalkyl having at least one oxygen, nitrogen, or sulfur atom within the ring, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted 4 to 6 membered heteroaryl having at least one oxygen, nitrogen, or sulfur atom in the ring, C_1-C_4 alkanoyl, or imide, wherein, if present, the substituent is at least one C_1-C_4 alkyl, cyano, fluoride, chloride, bromide, hydroxy, nitro, or thiol; and

[047] most preferably, R_1 and R_2 are each independently hydrogen, methyl, ethyl, propyl, isopropyl, sec-butyl, 3-methylbutyl, 2-methyl-2-propenyl, 2-propynyl, pentyl, hexyl, 2-butylyl, 2-hydroxy-2-(4-hydroxyphenyl)ethyl, 2-(2-pyridinyl)ethyl, 2-hydroxy-2-(3,4-dihydroxyphenyl)ethyl, 3-pyridinylmethyl, 2,5-difluorobenzyl, 4-trifluoromethoxyphenylmethyl, 3-methoxypropyl, 2-hydroxyethyl, 4-phenylbutyl,

2-phosphonatethyl, 3-(2-methyl)ethoxypropyl, 2-(2-thiophenyl)ethyl, N-benzyl-4-piperidinyl, 3-(1-pyrrolidinyl)propyl, 2-(N,N-diethyl)ethyl, tetrahydrofuranylmethyl, cyclopentyl, or cyclohexyl.

[048] R_4, $R_{4'}$, R_5, $R_{5'}$, R_8, $R_{8'}$, R_9, and $R_{9'}$ are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; and

[049] preferably, R_5, $R_{5'}$, R_9, and $R_{9'}$ are each independently hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, amine, C_1-C_4 alkylamine, C_1-C_4 amide, carboxylic acid, ester, halide, hydroxy, nitro, C_1-C_4 sulfide, C_1-C_4 sulfonyl, or sulfonamide;

[050] more preferably, R_5 and R_9 are each independently are hydrogen C_1-C_2 alkyl, C_1-C_2 alkoxy, amine, C_1-C_2 alkylamine, fluoride, chloride, bromide, hydroxy, nitro, C_1-C_2 sulfide, or C_1-C_2 sulfonyl;

[051] more preferably, $R_{5'}$ and $R_{9'}$ are each independently, hydrogen, C_1-C_2 alkyl, C_1-C_2 alkoxy, amine, C_1-C_2 alkylamine, C_1-C_2 amide, carboxylic acid, C_2-C_4 ester, or sulfonamide;

[052] most preferably, R_5 and R_9 are each independently are hydrogen, methyl, methoxy, thiomethyl, fluorine, chlorine, nitro, or methylsulfonyl; and

[053] most preferably, $R_{5'}$ and $R_{9'}$ are each independently, hydrogen, methyl, methyl ester, ethyl ester, C_1-C_2 amide, carboxylic acid, methoxy, or sulfonamide.

[054] R_6 is hydrogen, saturated or unsaturated,saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl or substituted or

unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, nitro, thiol, alkanoyl, imide, acetal, acetylene, aminal, amino acid, azo, diazo, carbamate, carboalkoxy ester, cyanohydrin, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, ketone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, sulfone, or sulfonic acid.

[055] preferably, R_6 is hydrogen, a C_1-C_8 straight chain or branched alkyl or substituted alkyl or unsaturated alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl,4 to 12 membered heterocycloalkyl or heteroaryl with at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is at least one hydroxy, halide, methoxy, ethoxy, carboxylic acid, ester, amine, or alkylamine;

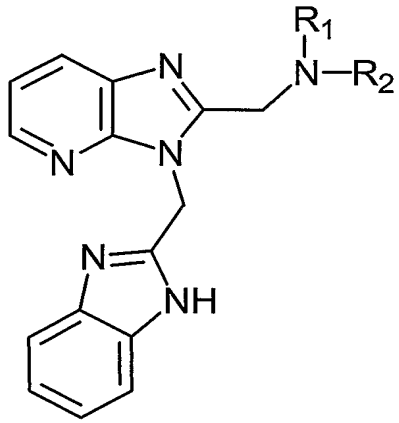
[056] more preferably, R_6 is hydrogen, a C_1-C_4 straight chain or branched alkyl or unsaturated alkyl, substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 5 to 6 membered aryl, substituted or unsubstituted 5 to 8 membered arylalkyl, or 4 to 9 membered heterocycloalkyl or heteroaryl with at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is at least one hydroxy, fluoride, chloride, bromide, methoxy, ethoxy, carboxylic acid, ester, amine, or C_1-C_4 alkylamine; and

[057] most preferably, R_6 is hydrogen, a benzyl, cyclopentyl, cyclohexyl, isopropyl, propyl, butyl, methylene cyclopropyl, methylene cyclobutyl, or benzimidazolyl.

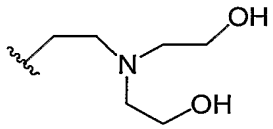
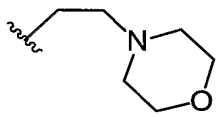
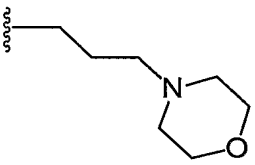
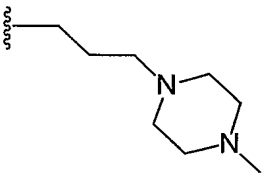
[058] In a preferred compound of Formula III, $R_{4'}$, $R_{5'}$, $R_{8'}$, $R_{9'}$ and R_6 are hydrogen. In another embodiment of the compounds of Formula III, at least one of R_4, $R_{4'}$, R_8, and $R_{8'}$ is not hydrogen. In another embodiment of the compounds of Formula III, at least two of R_4, $R_{4'}$, R_8, and $R_{8'}$ are not hydrogen. In another embodiment of the compounds of Formula III, at least three of R_4, $R_{4'}$, R_8, and $R_{8'}$ are not hydrogen. In another embodiment of the compounds of Formula III, at least one of R_5, $R_{5'}$, R_9, and $R_{9'}$ is not hydrogen. In another embodiment of the compounds of Formula III, at least two of R_5, $R_{5'}$, R_9, and $R_{9'}$ are not hydrogen. In another embodiment of the compounds of Formula III, at least three of R_5, $R_{5'}$, R_9, and $R_{9'}$ are not hydrogen.

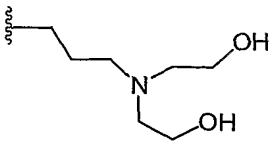
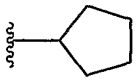
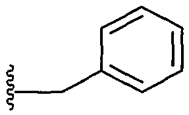
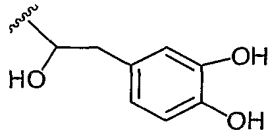
[059] The compounds of the invention encompassed by Formula III include compounds depicted in Formula V, including, but not limited to those contained within table 1. The specific compounds are for illustration and not limitation. Each compound in Table 1 has been prepared, isolated, purified, and tested for antiviral activity and cytotoxicity as discussed below.

TABLE 1

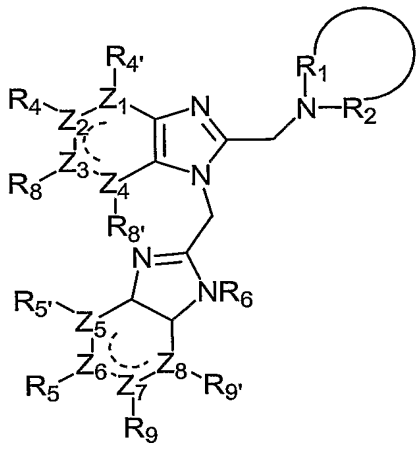


Formula V

Cmpd. #	R_1	R_2	PRA (IC_{50}) μg/mL	XTT (CC_{50}) μg/mL	^{1}H NMR 400MHz d_6-DMSO
1	-H		0.16	100	8.4 (1H, d), 8.2 (1H, d), 7.6 (2H, m), 7.4 (1H, m), 7.2 (2H, m), 5.90 (2H, s), 4.8 (2H, s), 3.8 (4H, t), 3.6 (4H, s), 3.3 (4H, t)
2	-H		0.24	100	8.4 (1H, d), 8.2 (1H, d), 7.6 (2H, m), 7.4 (1H, m), 7.2 (2H, m), 5.9 (2H, s), 4.8 (2H, s), 3.8 (4H, t), 3.5 (2H, t), 3.3 (2H, br), 3.1 (4H, br)
3	-CH_3	-$CH_2CH_2OCH_3$	0.15	100	8.4 (1H, d), 8.2 (1H, d), 7.6 (2H, m), 7.4 (1H, m), 7.2 (2H, m), 6.0 (2H, s), 5.0 (2H, s), 3.8 (2H, t), 3.6 (2H, t), 3.2 (3H, s), 3.0 (3H, s)
4	-H		0.19	100	8.4 (1H, d), 8.2 (1H, d), 7.6 (2H, m), 7.4 (1H, m), 7.2 (2H, m), 5.9 (2H, s), 4.8 (2H, s), 3.8 (4H, br), 3.3 (6H, m), 2.1 (2H, p)
5	-H		0.009	100	8.4 (1H, d), 8.2 (1H, d), 7.6 (2H, m), 7.4 (1H, m), 7.2 (2H, m), 5.9 (2H, s), 4.8 (2H, s), 3.5 (2H, br), 3.2 (4H, m), 2.8 (4H, s) 2.0 (2H, p)

Cmpd. #	R_1	R_2	PRA (IC_{50}) μg/mL	XTT (CC_{50}) μg/mL	^{1}H NMR 400MHz d_6-DMSO
6	-H		0.19	100	8.4 (1H, d), 8.2 (1H, d), 7.6 (2H, m), 7.4 (1H, m), 7.2 (2H, m), 5.9 (2H, s), 4.8 (2H, s), 3.8 (4H, t), 3.3 (8H, m), 2.2 (2H, p)
7	-H		0.004	100	8.4 (1H, d), 8.2 (1H, d), 7.6 (2H, m), 7.4 (1H, m), 7.2 (2H, m), 5.9 (2H, s), 4.8 (2H, s), 3.7 (1H, p), 2.1 (2H, m), 1.7 (4H, m), 1.6 (2H, br)
8	-$CH(CH_3)_2$		0.005	100	8.4 (1H, d), 8.2 (1H, d), 7.5 (4H, m), 7.4 (1H, m), 7.2 (5H, m), 5.8 (2H, s), 4.9 (2H, s), 4.5 (2H, s), 3.8 (1H, p), 1.4 (6H, d)
9	-CH_3	-$CH(CH_3)_2$	0.003	100	8.4 (1H, d), 8.2 (1H, d), 7.6 (2H, m), 7.4 (1H, m), 7.2 (2H, m), 6.0 (2H, s), 4.9 (2H, s), 3.9 (1H, p), 2.9 (3H, s), 1.4 (6H, d)
10	-$CH(CH_3)_2$		0.048	100	9.0 (1H, br), 8.4 (1H, d), 8.2 (1H, t), 7.6 (2H, m), 7.4 (1H, m), 7.2 (2H, m), 6.8-6.6 (3H, m), 6.0 (2H, dd) 5.1 (2H, s) 4.7 (1H, d), 4.0 (1H, p), 3.6 (1H, d), 3.4 (1H, t), 1.4 (6H, d)
11	-H	-$CH_2CH_2CH_2OCH_3$			8.4 (1H, d), 8.2 (1H, d), 7.6 (2H, m), 7.4 (1H, m), 7.2 (2H, m), 5.9 (2H, s), 4.8 (2H, s), 3.4 (2H, t), 3.2 (5H, m), 2.0 (2H, 5)
12	-$CH(CH_3)_2$	-$CH(CH_3)_2$	0.005	100	8.4 (1H, d), 8.2 (1H, d), 7.6 (2H, m), 7.4 (1H, m), 7.2 (2H, m), 6.0 (2H, s), 5.0 (2H, s), 3.9 (2H, p), 2.1 (2H, m), 1.4 (12H, d)

[060] In another preferred embodiment of the invention, with reference to Formula III, R_1 and R_2 are taken together to form a saturated or unsaturated nitrogen containing ring, the 1-position of the hetero-substituted benzimidazole moiety is substituted with a substituted or unsubstituted methylene-benzimidazole moiety, thus, the present invention encompasses compounds of the general Formula IV:



Formula IV

or a pharmaceutically-acceptable prodrug, salt, solvate including hydrate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof, wherein:

[061] Z_1, Z_2, Z_3 and Z_4 are each independently nitrogen or carbon and at least one of Z_1, Z_2, Z_3 and Z_4 is carbon;

[062] preferably one of Z_2 and Z_4 is nitrogen; more preferably Z_2 and Z_4 are both nitrogen and most preferably only Z_4 is nitrogen;

[063] Z_5, Z_6, Z_7 and Z_8 are each independently nitrogen or carbon;

[064] $-R_1-N-R_2-$ form a saturated or unsaturated substituted or unsubstituted heterocycloalkyl ring, substituted or unsubstituted heteroaryl ring, wherein, if present, the substituent is at least one substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkoxy, amides, sulfonamides, esters, hydroxy, halide, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, carbonyl, nitro, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl;

[065] preferably, $-R_1-N-R_2-$ form a saturated or unsaturated, substituted or unsubstituted 3 to 7 membered cycloalkyl, substituted or unsubstituted 3 to 7 membered heterocycloalkyl, substituted or unsubstituted 3 to 7 membered heteroaryl, wherein, if present, the substituent is at least one substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 alkoxy, C_1-C_4 esters, hydroxy, fluoride, chloride, bromide, substituted

or unsubstituted 3 to 8 membered aryl, substituted or unsubstituted 4 to 6 membered cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, carbonyl, or nitro; and

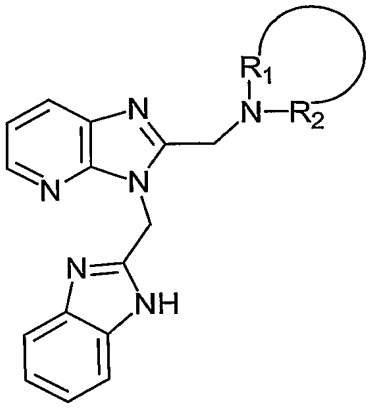
[066] more preferably, $-R_1-N-R_2-$ form a 5, 6, or 8 membered having at least one nitrogen atom, such as pyrrolidinyl, piperidinyl, optionally having a second atom which is nitrogen, oxygen, or sulfur atom, or at least one unsaturation, such as pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, piperazinyl, quinolinyl, acridinyl, thiazole, morpholinyl, and substituted with at least one methyl, ethyl, ester, methanol, 2-ethanol, aldehyde, substituted or unsubstituted aryl.

[067] R_4, $R_{4'}$, R_5, $R_{5'}$, R_6, R_8, $R_{8'}$, R_9, and $R_{9'}$ are as defined above for Formula III.

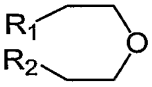
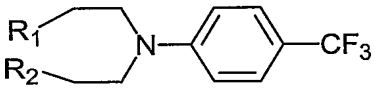
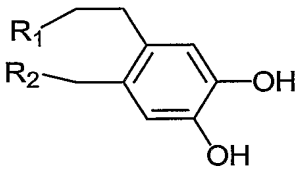
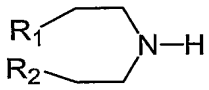
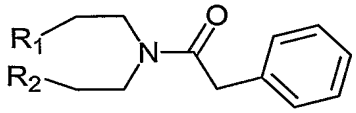
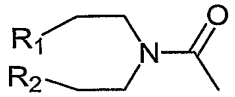
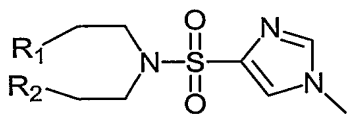
[068] In another embodiment of the compounds of Formula IV, $R_{4'}$, $R_{5'}$, $R_{8'}$, and $R_{9'}$ are hydrogen. In another embodiment of the compounds of Formula IV, at least two of R_4, $R_{4'}$, R_8, and $R_{8'}$ are not hydrogen. In another embodiment of the compounds of Formula IV, at least one of R_4, $R_{4'}$, R_8, and $R_{8'}$ is not hydrogen. In another embodiment of the compounds of Formula IV, at least three of R_4, $R_{4'}$, R_8, and $R_{8'}$ are not hydrogen. In another embodiment of the compounds of Formula IV, R_5, $R_{5'}$, R_9, and $R_{9'}$ are hydrogen. In another embodiment of the compounds of Formula IV, at least one of R_5, $R_{5'}$, R_9, and $R_{9'}$ is not hydrogen. In another embodiment of the compounds of Formula IV, at least two of R_5, $R_{5'}$, R_9, and $R_{9'}$ are not hydrogen. In another embodiment of the compounds of Formula IV, at least three of R_5, $R_{5'}$, R_9, and $R_{9'}$ are not hydrogen. In another embodiment of the compounds of Formula IV, R_6 is hydrogen.

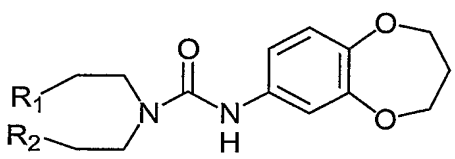
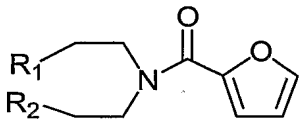
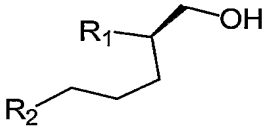
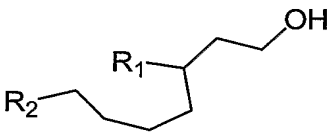
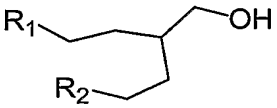
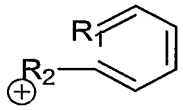
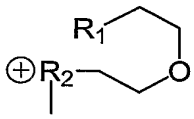
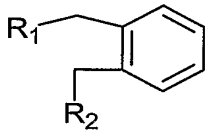
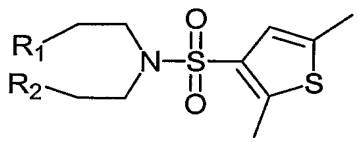
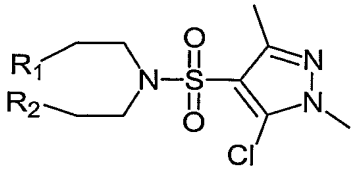
[069] The compounds of the invention encompassed by Formula IV include compounds of formula VI described in the header of Table 2, additional non-limiting specific compounds are contained within the table. The specific compounds are for illustration and not limitation. Each compound in Table 2 has been prepared, isolated, purified, and tested for antiviral activity and cytotoxicity as discussed below. For illustration purposes only, in Table 1, R_1 and R_2 represent bonds, for example, $R_1-CH_2CH_2CH_2-R_2$ represents a 4 membered including one nitrogen atom.

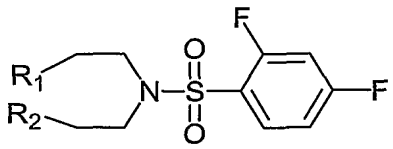
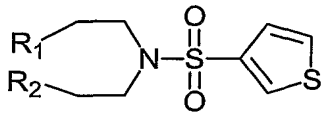
TABLE 2



Formula VI

Cmpd. #	R_1 and R_2	PRA (IC_{50}) μg/mL	XTT (CC_{50}) μg/mL	^{1}H NMR 400MHz d_6-DMSO
13		0.001	100	8.4 (1H, d), 8.2 (1H, d), 7.6 (2H, m), 7.4 (1H, m), 7.2 (2H, m), 6.0 (2H, s), 4.8 (2H, s), 3.7 (4H, s), 3.3 (4H, s)
14		0.005	100	8.4 (1H, d), 8.2 (1H, d), 7.6 (4H, d), 7.4 (1H, m), 7.2 (2H, m), 7.1 (2H, d), 6.0 (2H, s), 4.8 (2H, s), 3.5 (8H, d)
15		0.013	100	8.4 (1H, d), 8.2 (1H, d), 7.6 (2H, m), 7.2 (4H, m), 6.7 (1H, s), 6.5 (1H, s), 6.0 (2H, s), 5.0 (2H, s), 4.4 (2H, s), 3.7 (2H, m), 3.0 (2H, t)
16		0.12	100	8.6 (1H, br), 8.3 (1H, d), 8.1 (1H, d), 7.6 (2H, m), 7.4 (3H, m), 6.0 (2H, s), 4.0 (2H, s), 2.7 (4H, s), 2.6 (4H, s)
17		0.02	100	8.4 (1H, d), 8.2 (1H, d), 7.6 (2H, m), 7.4 (1H, m), 7.2 (7H, m), 6.0 (2H, s), 4.6 (2H, s), 3.7 (2H, s), 3.5 (4H, br), 3.1 (4H, s)
18		0.004	100	8.4 (1H, d), 8.2 (1H, d), 7.6 (2H, m), 7.4 (1H, m), 7.3 (2H, m), 6.0 (2H, s), 4.7 (2H, s), 3.6 (4H, br), 3.2 (4H, d), 2.0 (3H, s)
19			100	

Cmpd. #	R_1 and R_2	PRA (IC_{50}) μg/mL	XTT (CC_{50}) μg/mL	^{1}H NMR 400MHz d_6-DMSO
20		0.005	100	8.6 (1H, s), 8.4 (1H, d), 8.2 (1H, s), 7.6 (2H, d), 7.4 (1H, m), 7.3 (2H, m), 7.1 (1H, s), 7.0 (1H, d), 6.8 (1H, d), 6.0 (2H, s), 4.7 (2H, s), 4.0 (4H, m), 3.6 (4H, s), 3.2 (4H, s), 2.0 (2H, p)
21		0.013	100	8.4 (1H, d), 8.2 (1H, d), 7.9 (1H, s), 7.6 (2H, m), 7.4 (1H, m), 7.2 (2H, m), 7.0 (1H, d), 6.6 (1H, m), 6.0 (2H, s), 4.6 (2H, s), 3.7 (4H, br), 3.2 (4H, s)
22		0.002	100	8.4 (1H, d), 8.2 (1H, d), 7.6 (2H, m), 7.4 (1H, m), 7.2 (2H, m), 6.0 (2H, s), 5.1 (2H, dd), 4.0 (1H, m), 3.6 (4H, m), 2.3-1.8 (4H, q of m)
23		0.01	100	8.4 (1H, d), 8.2 (1H, d), 7.6 (2H, m), 7.4 (1H, m), 7.2 (2H, m), 6.0 (2H, s), 5.0 (2H, dd), 3.8 (1H, br), 3.5 (3H, m), 3.4 (1H, br), 2.2-1.6 (8H, m)
24		0.009	100	8.4 (1H, d), 8.2 (1H, d), 7.6 (2H, m), 7.4 (1H, m), 7.2 (2H, m), 6.0 (2H, s), 5.0 (2H, s), 3.8 (2H, m), 3.2-3.0 (4H, m), 2.1-1.8 (4H, m) 1.2 (1H, q)
25		0.4	100	9.3 (2H, d), 8.7 (1H, t), 8.4 (1H, d), 8.2 (2H, t), 8.1 (1H, d), 7.5 (4H, d), 7.3 (1H, m), 7.2 (2H, m), 6.4 (2H, s), 6.0 (2H, s)
26		1.0	100	8.4 (1H, d), 8.2 (1H, d), 7.6 (2H, m), 7.4 (1H, m), 7.2 (2H, m), 6.0 (2H, s), 5.3 (2H, s), 4.0 (4H, m), 3.9 (2H, m), 3.6 (2H, d), 3.4 (3H, s)
27		0.02	100	8.4 (1H, d), 8.2 (1H, d), 7.5 (5H, m), 7.2 (4H, m), 6.0 (2H, s), 5.2 (2H), 4.9 (2H, s)
28		0.016	100	8.4 (1H, d), 8.2 (1H, d), 7.4 (3H, m), 7.3 (2H, m), 6.8 (1H, s), 6.0 (2H, s), 4.4 (2H, s), 3.0 (8H, br), 2.4 (3H, s)
29		0.2	100	8.4 (1H, d), 8.2 (1H, d), 7.4 (3H, m), 7.2 (2H, m), 6.0 (2H, s), 4.2 (2H, s), 3.8 (3H, s), 2.8 (8H, br), 2.2 (3H, s)

Cmpd. #	R_1 and R_2	PRA (IC_{50}) μg/mL	XTT (CC_{50}) μg/mL	^{1}H NMR 400MHz d_6-DMSO
30		0.01	100	8.4 (1H, d), 8.2 (1H, d), 7.7 (2H, m), 7.4-7.2 (6H, m), 6.0 (2H, s), 4.2 (2H, s), 2.7 (8H, s)
31		0.01	100	8.4 (1H, d), 8.2 (1H, s), 8.1 (1H, d), 7.9 (1H, m), 7.4-7.2 (6H, m), 6.0 (2H, s), 4.4 (2H, s), 3.0 (8H, d)

[070] The compounds of the invention can contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (*i.e.*, geometric isomers), enantiomers, or diastereomers. According to the invention, the chemical structures depicted herein, and therefore the compounds of the invention, encompass all of the corresponding enantiomers and stereoisomers, that is, both the stereomerically pure form (*e.g.*, geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures.

[071] A compound of the invention is considered optically active or enantiomerically pure (*i.e.*, substantially the R-form or substantially the S-form) with respect to a chiral center when the compound is about 90% ee (enantiomeric excess) or greater, preferably, equal to or greater than 95% ee with respect to a particular chiral center. A compound of the invention is considered to be in enantiomerically-enriched form when the compound has an enantiomeric excess of greater than about 1% ee, preferably greater than about 5% ee, more preferably, greater than about 10% ee with respect to a particular chiral center. As used herein, a racemic mixture means about 50% of one enantiomer and about 50% of is corresponding enantiomer relative to all chiral centers in the molecule. Thus, the invention encompasses all enantiomerically-pure, enantiomerically-enriched, and racemic mixtures of compounds of Formulas I through VI.

[072] Enantiomeric and stereoisomeric mixtures of compounds of the invention can be resolved into their component enantiomers or stereoisomers by well-known methods. Examples include, but are not limited to, the formation of chiral salts and the use of chiral or high performance liquid chromatography "HPLC" and the formation and crystallization of chiral salts. See, *e.g.*, Jacques, J., *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen, S. H., *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of

Notre Dame Press, Notre Dame, IN, 1972); *Stereochemistry of Organic Compounds*, Ernest L. Eliel, Samuel H. Wilen and Lewis N. Manda (1994 John Wiley & Sons, Inc.), and *Stereoselective Synthesis A Practical Approach*, Mihály Nógrádi (1995 VCH Publishers, Inc., NY, NY). Enantiomers and stereoisomers can also be obtained from stereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

4.2 General Synthetic Methodology

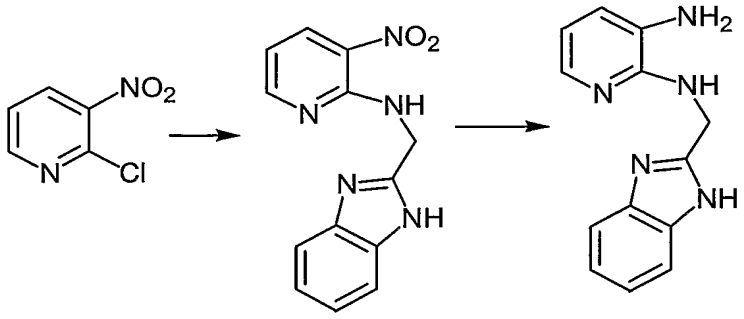
[073] The compounds of the invention can be obtained via standard, well-known synthetic methodology. Some convenient methods are illustrated in Schemes **1-2**. These schemes are merely meant to be illustrative of one synthetic pathway, however, these synthetic pathways can be modified in ways that will be obvious to those skilled in the art to create a variety of hetero-substituted benzimidazole compounds. Starting materials useful for preparing the compounds of the invention and intermediates therefore, are commercially available or can be prepared from commercially available materials using known synthetic methods and reagents. Such starting materials include, but are not limited to, 2-(chloromethyl)benzimidazole, 2-chlorobenzimidazole, 3,4-diaminobenzoic acid, 1-fluoro-2-nitrobenzene, and 3-fluoro-4-nitrotoluene, and amines. Amines include, but are not limited to, diisopropylamine, pyrrolidin-2-ylmethanol, 1-(3-trifluoromethylphenyl)-piperazine, piperidin-3-ylmethanol, morpholine, cyclohexyl-ethylamine, 1-(1*H*-pyrrol-2-yl)piperazine, and 1-(3-trifluoromethylphenyl)piperazine. Compounds used in the syntheses are commercially available from Aldrich Chemical Co. (Milwaukee, Wisconsin), Sigma® (St. Louis, Missouri), Fluka (Milwaukee, Wisconsin), and Maybridge (Cornwall, England).

[074] Methods of synthesizing the compounds of the present invention are illustrated in the following schemes. Because of possible discrepancies in using chemical nomenclature where structures are provided for compounds or moieties the structure controls the definition of the compound or moiety, and not the chemical name. Representative synthetic schemes for the compounds of Tables 1 and 2 are shown below.

4.2.1 Synthesis of 1-methylbenzimidazole substituted Hetero-substituted-benzimidazoles

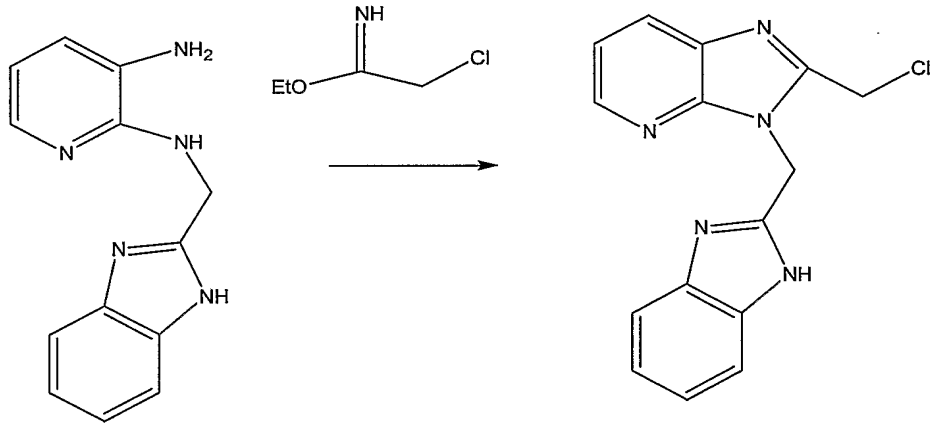
[075] One method to synthesize the hetero-substituted benzimidazole compounds of Formula III is to allow 2-Chloro-3-nitropyridine to react in the presence of Aminomethylbenzimidazole hydrochloride and diisopropylethyl amine to form N^2-(1H-Benzoimidazol-2-ylmethyl)-pyridine-2,3-diamine, after reduction. as depicted in

scheme 1. Optionally, the ring nitrogen can be protected using protecting groups commonly known in the art, such as *t*-Boc.



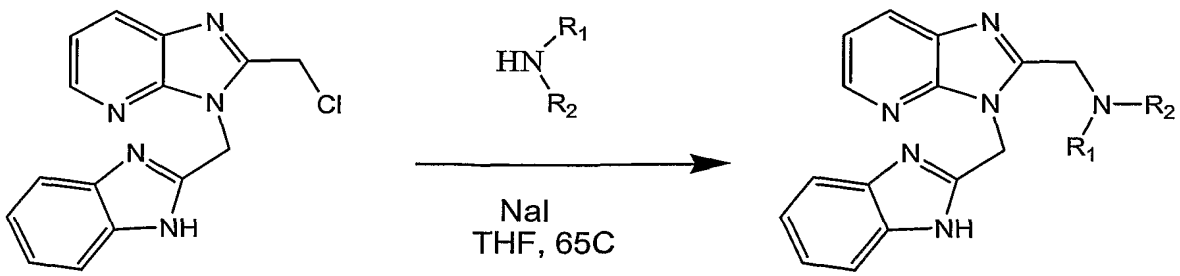
Scheme 1

Thereafter, N^2-(1H-Benzoimidazol-2-ylmethyl)-pyridine-2,3-diamine is reacted with methyl-chloro ethyl imidate at 65°C for 12 hours to form 3-(1H-Benzoimidazol-2-ylmethyl)-2-chloromethyl-3H-imidazo[4,5-b]pyridine as depicted in scheme 2.



Scheme 2

Finally, the 3-(1H-Benzoimidazol-2-ylmethyl)-2-chloromethyl-3H-imidazo[4,5-b]pyridine is allowed to react with a secondary amine in the presence of a base to obtain the compounds of Formula III, as depicted in Scheme 3. In Scheme 3, Benzimidazole-deazapurine methyl chloride and NaI are dissolved in anhydrous THF. To this solution amine is added and heated at 65°C for 3 hours. The resulting materials are acidified with trifluoroacetic acid and purified by reverse phase HPLC on a 1" C18 column. Optionally, the compounds are isolated by methods commonly used in the art, such as column chromatography, liquid chromatography, high pressure chromatography, among others.



Scheme 3

[076] Optionally, depending upon the reaction conditions, the nitrogen at the 1-position of substituted or unsubstituted benzimidazole compounds can be protected from further reacting prior to allowing the benzimidazole compound with other reagents.

4.3 Prophylactic and Therapeutic Uses

[077] The invention encompasses the discovery of a novel hetero-substituted benzimidazoles that are potent and selective antivirals. In particular, the compounds of the invention are selective for virally infected cells and thus have little or no cytotoxicity for healthy cells. As described in Section 5, the compounds within the invention were tested for both inhibitory concentrations (*e.g.*, IC_{50}) and cytotoxicity concentration (*e.g.*, CC_{50}). Clearly, such compounds are particularly useful *in vivo* for the treatment or prevention of viral-mediated diseases or infections, particularly for RSV infections.

[078] The IC_{50} data is the concentration (μM) of the compounds that inhibits viral replication by about 50% relative to viral replication in the absence of the hetero-substituted benzimidazole compound of the invention. The CC_{50} data is the concentration (μM) of the compound that kills 50% of the healthy cells relative to amount of healthy cell death in the absence of the hetero-substituted benzimidazole compound of the invention. The selective index (SI) is the ratio of the CC_{50}/IC_{50}.

[079] In one embodiment, the hetero-substituted benzimidazole compound has an IC_{50} less than 1.0 μM. In preferred embodiments, the hetero-substituted benzimidazole compound has an IC_{50} of less than 1.0 μM, less than 0.9 μM, less than 0.8 μM, less than 0.7 μM, less than 0.6 μM, less than 0.5 μM, less than 0.4 μM, less than 0.3 μM, less than 0.2 μM, less than 0.1 μM, less than 0.09 μM, less than 0.08 μM, less than 0.07 μM, less than 0.06 μM, less than 0.05 μM, less than 0.04 μM, less than 0.03 μM, less than 0.02 μM, less than 0.01 μM, less than 0.005, or less than 0.0001. In one embodiment of the invention, the hetero-substituted benzimidazole compound has an IC_{50} from about 0.1 μM to about 0.5 μM, preferably from about 0.5 μM to about 0.01 μM, and most preferably from about 0.005 μM to about 0.01 μM. In other preferred embodiments, the IC_{50} of the hetero-substituted

benzimidazole compound is no greater than 10 μM, preferably no greater than 8 μM, more preferably no greater than 5 μM, most preferably no greater than 3 μM.

[080] In another embodiment, the hetero-substituted benzimidazole compound has a CC_{50} greater than 10 μM. In certain embodiments of the invention, the hetero-substituted benzimidazole compound has a CC_{50} greater than 20 μM, greater than 30 μM, greater than 35 μM, greater than 40 μM, greater than 45 μM, greater than 50 μM, greater than 55 μM, greater than 60 μM, greater than 65 μM, greater than 70 μM, greater than 75 μM, greater than 80 μM, greater than 85 μM, greater than 90 μM, greater than 95 μM, greater than 100 μM, greater than 110 μM, greater than 120 μM, greater than 130 μM, greater than 140 μM, greater than 150 μM, and greater than 200 μM. In one embodiment of the invention, the hetero-substituted benzimidazole compound has a CC_{50} from about 20 μM to about 50 μM, preferably from about 50 μM to about 100 μM, and most preferably from about 100 μM to about 150 μM.

[081] The unique Selective Index (SI) for each compound can be calculated as the inhibitory concentration (IC_{50}) divided by the cytotoxic concentration (CC_{50}). The compounds of the invention which are particularly useful are the selective compounds, most particularly useful are the compounds with an Selective Index (SI) above 20, preferably above 50, including compounds with SI's greater than 10,000. In one embodiment, the hetero-substituted benzimidazole compound has an SI from about 50 to 6000, preferably greater than 100, and more preferably greater than 500, and most preferably greater than 1000.

[082] The present invention encompasses methods for treating, ameliorating or preventing one or more symptoms associated with a viral infection, comprising the administration to a subject (*e.g.*, a mammal, preferably a human) in need of such treatment or prevention a therapeutically or prophylactically effective amount of a hetero-substituted benzimidazole compound of the invention. In various embodiments, a subject is administered a therapeutically or prophylactically effective amount of a hetero-substituted benzimidazole compound of the invention or a pharmaceutically acceptable prodrug, salt, solvate, hydrate or clathrate thereof.

[083] The present invention also encompasses methods for treating, ameliorating or preventing one or more symptoms associated with a viral infection by inhibiting viral membrane fusion associated events, comprising the administration of a therapeutically or prophylactically effective amount of a hetero-substituted benzimidazole compound of the invention. In certain embodiments, a hetero-substituted benzimidazole compound prevents a virus from fusing, attaching or inserting into its host cell's membrane. In other

embodiments, a combination of hetero-substituted benzimidazole compounds prevent a virus from fusing, attaching or inserting into its host cell's membrane.

[084] The antifusogenic capability of the hetero-substituted benzimidazole compounds of the invention may additionally be utilized to inhibit or treat/ameliorate symptoms caused by processes involving membrane fusion events. Such events may include, for example, virus transmission via cell-cell fusion and abnormal neurotransmitter exchange via cell-fusion. In preferred embodiments, the hetero-substituted benzimidazole compounds of the invention may be used to inhibit free viral transmission to uninfected cells wherein such viral infection involves membrane fusion events or involves fusion of a viral structure with a cell membrane.

[085] In alternative embodiments, a hetero-substituted benzimidazole compound of the present invention inhibits or downregulates viral replication. The hetero-substituted benzimidazole compound inhibits or downregulates viral replication by at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to viral replication in the absence of said hetero-substituted benzimidazole compounds. In other embodiments, a combination of hetero-substituted benzimidazole compounds inhibit or downregulate viral replication. Viral replication is inhibited or downregulated by at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to viral replication in the absence of said hetero-substituted benzimidazole compounds. The ability of one or more hetero-substituted benzimidazoles of the invention to inhibit or downregulate viral replication may be determined by techniques described herein or otherwise known in the art. For example, the inhibition or downregulation of viral replication can be determined by detecting the viral titer in the tissues or body fluids of a subject.

[086] In another embodiment, a subject is administered one or more hetero-substituted benzimidazole compounds of the present invention for the treatment, prevention or amelioration of one or more symptoms associated with a viral infection in an amount effective for decreasing viral titers. In yet another embodiment, a subject is administered a dose of a hetero-substituted benzimidazole compound of the present invention for the treatment or amelioration of one or more symptoms associated with a viral infection in an amount effective to reduce the severity or length of the viral infection or the dose effectively administered to a cotton rat that results in a viral titer in the rat 5 days after challenge with

10^5 pfu of virus that is 99% lower than the viral titer 5 days after challenge with 10^5 pfu of virus in a cotton rat not administered the dose prior to challenge.

[087] In yet other embodiments, the compounds of the invention are administered to decrease viral load. One or more hetero-substituted benzimidazole compounds reduces viral load by at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to viral load in the absence of said hetero-substituted benzimidazole compounds. The ability of one or more hetero-substituted benzimidazoles of the invention to reduce viral load may be determined by techniques described herein or otherwise known in the art. For example, the reduction in viral load can be determined by detecting the change in viral titer in the tissues or body fluids of a subject.

[088] With respect to antiviral activity, the compounds of the invention inhibit the transmission of RSV. Accordingly, in a preferred embodiment, the present invention encompasses the administration of compounds of the invention for the inhibition of RSV transmission. The compounds of the invention also inhibit HPIV, hMPV and influenza viruses. Accordingly, in other preferred embodiments, the present invention encompasses the administration of compounds of the invention for the inhibition of HPIV transmission, hMPV and influenza virus transmission.

[089] Also encompassed by the invention is the administration of compounds of the invention with antiviral activity against human retroviruses, such as but not limited to the human T-lymphocyte viruses (HTLV-I and II), and non-human retroviruses such as but not limited to, bovine leukosis virus, feline sarcoma and leukemia viruses, sarcoma and leukemia viruses, and sheep progress pneumonia viruses. Also encompassed is the administration of the compounds of the invention with antiviral activity against non-retroviral viruses such as but not limited to human respiratory syncytial virus, canine distemper virus, newcastle disease virus, human parainfluenza virus, influenza viruses, measles viruses, Epstein-Barr viruses, hepatitis B viruses, ebola virus and simian Mason-Pfizer viruses. Further encompassed by the invention is the administration of the compounds of the invention with antiviral activity against non-enveloped viruses including but are not limited to picornaviruses such as polio viruses, hepatitis A virus, enterovirus, echoviruses and coxsackie viruses, papovaviruses such as papilloma virus, parvoviruses, adenoviruses and reoviruses.

[090] In specific embodiments, the present invention is directed to therapies which involve administering hetero-substituted benzimidazole compounds of the invention to a

subject, for preventing, treating, or ameliorating one or more symptoms associated with a RSV infection. In particular, the invention encompasses methods for treating, preventing or ameliorating one or more symptoms associated with infections of the upper and/or lower respiratory tract, particularly those caused by RSV infection. Symptoms include but are not limited to influenza-like illnesses, persistent cold-like symptoms, cough, rhinities, mild fever, wheezing, severe cough, increased respiratory rate, symptoms associated with bronchiolitis and/or pneumonia, infection of the lungs, and exacerbation of other lung pathologies such as asthma and otitis media.

[091] In other specific embodiments, the present invention is directed to therapies which involve administering hetero-substituted benzimidazole compounds of the invention to a subject, for preventing, treating, or ameliorating one or more symptoms associated with a HPIV or hMPV infection. In particular, the invention encompasses methods for treating, preventing or ameliorating symptoms associated with infections of the upper and/or lower respiratory tract, particularly those caused by HPIV or hMPV infection. Symptoms include but are not limited to influenza-like illnesses, symptoms associated with bronchitis, bronchiolitis and/or pneumonia, infection of the lungs, and exacerbation of other lung pathologies such as asthma. In yet other embodiments, the present invention is directed to therapies which involve administering hetero-substituted benzimidazole compounds of the invention to a subject, for preventing, treating, or ameliorating one or more symptoms associated with influenza.

[092] Hetero-substituted benzimidazole compounds of the present invention that function as inhibitors of membrane fusion can be administered to a subject, to treat, prevent or ameliorate one or more symptoms associated with a RSV infection. For example, hetero-substituted benzimidazole compounds which disrupt or prevent the fusion a RSV virus and its host cell may be administered to a subject, to treat, prevent or ameliorate one or more symptoms associated with a RSV infection.

[093] In a specific embodiment, a hetero-substituted benzimidazole compound prevents RSV from fusing, attaching or inserting into its host cell's membrane. In another embodiment, a combination of hetero-substituted benzimidazole compounds prevents RSV from fusing, attaching or inserting into its host cell's membrane.

[094] Also contemplated by the invention is the administration of one or more hetero-substituted benzimidazole compounds of the invention that function as inhibitors of membrane fusion to a subject to treat, prevent or ameliorate one or more symptoms associated with an HPIV or hMPV infection or influenza.

[095] In a specific embodiment, a hetero-substituted benzimidazole compound prevents HPIV, hMPV or influenza virus from fusing, attaching or inserting into its host cell's membrane. Thus, one or more hetero-substituted benzimidazole compounds of the invention can be used to simultaneously treat or prevent HPIV, hMPV, influenza virus or RSV infection in a patient in need thereof. In another embodiment, a combination of hetero-substituted benzimidazole compounds prevents HPIV, hMPV or influenza virus from fusing, attaching or inserting into its host cell's membrane.

[096] In other specific embodiments, a hetero-substituted benzimidazole compound of the present invention inhibits or downregulates RSV replication. RSV replication is inhibited or downregulated by at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to RSV replication in the absence of said hetero-substituted benzimidazole compounds. In another embodiment, a combination of hetero-substituted benzimidazole compounds inhibit or downregulate RSV replication. RSV replication is inhibited or downregulated by at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to RSV replication in the absence of said hetero-substituted benzimidazole compounds. The ability of one or more hetero-substituted benzimidazoles of the invention to inhibit or downregulate RSV replication may be determined by techniques described herein or otherwise known in the art. For example, the inhibition or downregulation of viral replication can be determined by detecting the RSV titer in the lungs of a subject.

[097] In yet other specific embodiments, a hetero-substituted benzimidazole compound of the present invention inhibits or downregulates HPIV, hMPV or influenza virus replication. HPIV, hMPV or influenza virus replication is inhibited or downregulated by at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to viral replication in the absence of said hetero-substituted benzimidazole compounds. In another embodiment, a combination of hetero-substituted benzimidazole compounds inhibit or downregulate HPIV, hMPV or influenza virus replication. HPIV, hMPV or influenza virus replication is inhibited or downregulated by at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to viral replication in the

absence of said hetero-substituted benzimidazole compounds. The ability of one or more hetero-substituted benzimidazoles of the invention to inhibit or downregulate HPIV, hMPV or influenza virus replication may be determined by techniques described herein or otherwise known in the art. For example, the inhibition or downregulation of viral replication can be determined by detecting the viral titer in the lungs of a subject.

[098] In a preferred embodiment, one or more hetero-substituted benzimidazole compounds of the invention are administered to a immunocompromised subject to treat, prevent or ameliorate one or more symptoms associated with RSV infection. In specific embodiments, one or more hetero-substituted benzimidazole compounds of the invention are administered to a human with cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency or acquired immunodeficiency, or to a human who has had a bone marrow transplant to treat, prevent or ameliorate one or more symptoms associated with RSV infection. In other embodiments, one or more hetero-substituted benzimidazole compounds of the invention are administered to a human undergoing cardiac, renal and lung transplants or to a human with leukemia. In other embodiments, one or more hetero-substituted benzimidazole compounds of the invention are administered to a human infant, preferably a human infant born prematurely or a human infant at risk of hospitalization for RSV infection to treat, prevent or ameliorate one or more symptoms associated with RSV infection. In yet other embodiments, one or more hetero-substituted benzimidazole compounds of the invention are administered to the elderly or people institutionalized or in group homes (*e.g.*, nursing homes or rehabilitation centers).

[099] In other preferred embodiments, one or more hetero-substituted benzimidazole compounds of the invention are administered to a subject with symptoms common to RSV, HPIV, hMPV or influenza virus infections. In particular, where there is difficulty diagnosing the viral infection causing the respiratory symptoms, one or more hetero-substituted benzimidazole compounds of the invention are administered to a subject in need of such treatment.

[0100] In a specific embodiment, a subject is administered one or more hetero-substituted benzimidazole compounds of the present invention for the treatment, prevention or amelioration of one or more symptoms associated with a RSV infection in an amount effective for decreasing RSV titers. In accordance with this embodiment, an effective amount of one or more hetero-substituted benzimidazole compounds reduces the RSV titers in the lung as measured, for example, by the concentration of RSV in sputum samples or a lavage from the lungs from the subject in need of such treatment.

[0101] In yet another embodiment, a subject is administered a dose of a hetero-substituted benzimidazole compound of the present invention for the treatment or amelioration of one or more symptoms associated with a RSV infection in an amount effective to reduce the severity or length of RSV infection or the dose effectively administered to a cotton rat that results in a RSV titer in the rat 5 days after challenge with 10^5 pfu RSV that is 99% lower than the RSV titer 5 days after challenge with 10^5 pfu of RSV in a cotton rat not administered the dose prior to challenge.

[0102] In another embodiment, a subject is administered a dose of a hetero-substituted benzimidazole compound of the present invention for the treatment or amelioration of one or more symptoms associated with a RSV infection in an amount effective to reduce the viral load of the subject. In yet another embodiment a subject is administered a dose of a hetero-substituted benzimidazole compound of the present invention for the treatment or amelioration of one or more symptoms associated with a HPIV, hMPV infection or influenza in an amount effective to reduce the viral load of the subject.

[0103] Preferably, the dose of the hetero-substituted benzimidazole compound of the present invention is 5 to 50 mg/kg/day, more preferably 10 to 40 mg/kg/day, most preferably 15 to 30 mg/kg/day. Administration may be made daily in either single or divided doses and the administration may be chronic or acute depending upon the use or disease to be treated or prevented.

[0104] Hetero-substituted benzimidazole compounds of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein below. In various embodiments, therapeutic or pharmaceutical compositions comprising hetero-substituted benzimidazole compounds of the invention are administered to a subject, to treat, prevent or ameliorate one or more symptoms associated with a viral infection. In preferred embodiments, the symptoms are associated with RSV infection.

[0105] In specific embodiments, therapeutic or pharmaceutical compositions comprising hetero-substituted benzimidazole compounds of the invention are administered to a human with cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency or acquired immunodeficiency, or to a human who has had a bone marrow transplant to treat, prevent or ameliorate one or more symptoms associated with RSV infection. In other embodiments, therapeutic or pharmaceutical compositions comprising hetero-substituted benzimidazole compounds of the invention are administered to a human infant, preferably a human infant born prematurely or a human infant at risk of hospitalization for RSV infection to treat, prevent or ameliorate one or more symptoms

associated with RSV infection. In yet other embodiments, therapeutic or pharmaceutical compositions comprising hetero-substituted benzimidazole compounds of the invention are administered to the elderly or people in group homes (*e.g.*, nursing homes or rehabilitation centers).

[0106] In a specific embodiment, a subject is administered a therapeutic or pharmaceutical composition comprising one or more hetero-substituted benzimidazole compounds of the present invention for the treatment, prevention or amelioration of one or more symptoms associated with a RSV infection in an amount effective for decreasing RSV titers. In accordance with this embodiment, an effective amount of a pharmaceutical composition of the invention reduces the RSV titers in the lung as measured, for example, by the concentration of RSV in sputum samples or a lavage from the lungs from a subject.

4.3.1 Effective Dose

[0107] Toxicity and therapeutic efficacy of the compounds of the invention can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50}. Compounds that exhibit large therapeutic indices are preferred. While compounds that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

[0108] The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC_{50} (*i.e.*, the concentration of the test compound that achieves a half-maximal inhibition of symptoms, *e.g.*, fusogenic events or viral infection, relative to the amount of the symptoms in the absence of the test compound) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography (HPLC).

4.4 Methods of Administration of Hetero-substituted Benzimidazole Compounds

[0109] The invention provides any method of administering an effective amount of a novel hetero-substituted benzimidazole compound or pharmaceutical composition of the invention for the treatment, prophylaxis, or amelioration of one or more symptoms associated with a viral infection.

[0110] In particular embodiments, the invention provides for any method of administrating a novel hetero-substituted benzimidazole compound of the invention for the prevention, treatment or amelioration of one or more symptoms associated with a RSV infection. As discussed herein below, novel hetero-substituted benzimidazole compounds of the invention can be administered by oral, parenteral (intravenous, intramuscular, subcutaneous, Bolus injection), transdermal, mucosal (rectal, vaginal, buccal, sublingual) administration, preferably by oral or pulmonary administration (inhalation by aerosols or other known methods).

[0111] In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion, by injection, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

[0112] In another embodiment, the composition can be delivered in a vesicle, in particular a liposome (see Langer, *Science* 249:1527-1533 (1990); Treat *et al.*, in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, ibid., pp. 3 17-327; see generally ibid.).

Various delivery systems are known and can be used to administer a hetero-substituted benzimidazole compound of the invention, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, receptor-mediated endocytosis (see, *e.g.*, Wu and Wu, *J. Biol. Chem.* 262:4429-4432 (1987)), etc. Methods of administering a hetero-substituted benzimidazole compound include, but are not limited to, parenteral administration (*e.g.*, intradermal, intramuscular, intraperitoneal, intravenous and subcutaneous), epidural, and mucosal (*e.g.*, intranasal and oral routes). In a specific embodiment, hetero-substituted benzimidazole compounds of the present invention or derivatives thereof, or pharmaceutical compositions are administered intramuscularly, intravenously, or subcutaneously. The compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral

mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local.

[0113] Preferably, pulmonary administration is employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent. See, *e.g.*, U.S. Patent Nos. 5,985,320, 5,985,309, 5,934,272, 5,874,064, 5,855,913, and 5,290,540; and PCT Publication Nos. WO 92/19244, WO 97/32572, WO 97/44013, WO 98/31346, and WO 99/66903, each of which is incorporated herein by reference their entirety. In a preferred embodiment, an hetero-substituted benzimidazole compound of the invention or composition of the invention is administered using Alkermes AIR™ pulmonary drug delivery technology (Alkermes, Inc., Cambridge, MA).

[0114] In other embodiments, the composition can be delivered using a surface active material and instilling or spraying the resulting suspension into the airway of a subject as described in U.S. Patent No. 4,397,839 which is incorporated by reference in its entirety.

[0115] In yet another embodiment, the composition can be delivered in a controlled release or sustained release system. In one embodiment, a pump may be used to achieve controlled or sustained release (see Langer, *supra*; Sefton, 1987, *CRC Crit. Ref. Biomed. Eng.* 14:20; Buchwald *et al.*, 1980, *Surgery* 88:507; Saudek *et al.*, 1989, *N. Engl. J. Med.* 321:574). In another embodiment, polymeric materials can be used to achieve controlled or sustained release of the hetero-substituted benzimidazole compounds of the invention or derivatives thereof (see *e.g.*, Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, 1983, *J., Macromol. Sci. Rev. Macromol. Chem.* 23:61; see also Levy *et al.*, 1985, *Science* 228:190; During *et al.*, 1989, *Ann. Neurol.* 25:351; Howard *et al.*, 1989, *J. Neurosurg.* 7 1:105); U.S. Patent No. 5,679,377; U.S. Patent No. 5,916,597; U.S. Patent No. 5,912,015; U.S. Patent No. 5,989,463; U.S. Patent No. 5,128,326; PCT Publication No. WO 99/15154; and PCT Publication No. WO 99/20253. Examples of polymers used in sustained release formulations include, but are not limited to, poly(2-hydroxy ethyl methacrylate), poly(methyl methacrylate), poly(acrylic acid), poly(ethylene-co-vinyl acetate), poly(methacrylic acid), polyglycolides (PLG), polyanhydrides, poly(N-vinyl pyrrolidone), poly(vinyl alcohol), polyacrylamide, poly(ethylene glycol), polylactides (PLA), poly(lactide-co-glycolides) (PLGA), and polyorthoesters. In a preferred embodiment, the polymer used in a sustained release formulation is inert, free of leachable impurities, stable on storage, sterile, and biodegradable. In yet another embodiment, a

controlled or sustained release system can be placed in proximity of the therapeutic target, *i.e.*, the lungs, thus requiring only a fraction of the systemic dose (see, *e.g.*, Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)).

[0116] Controlled release systems are discussed in the review by Langer (1990, *Science* 249:1527-1533). Any technique known to one of skill in the art can be used to produce sustained release formulations comprising one or more hetero-substituted benzimidazole compounds of the invention and are discussed hereinbelow in Section 4.5 in more detail.

4.5 Pharmaceutical Compositions

[0117] Pharmaceutical compositions can be used in the preparation of unit dosage forms. Accordingly, pharmaceutical compositions and dosage forms of the invention comprise one or more of the novel hetero-substituted benzimidazole compounds disclosed herein, or a pharmaceutically acceptable prodrug, polymorph, salt, solvate, hydrate, or clathrate thereof. The invention encompasses pharmaceutical compositions and unit dosage forms comprising at least one compound of general Formula I-VI, preferably a hetero-substituted benzimidazole of general Formula III, IV, V, or VI or a pharmaceutically acceptable prodrug, polymorph, salt, solvate, hydrate, clathrate, hydrate salt, or solvate salt thereof. Pharmaceutical compositions and dosage forms of the invention typically also comprise one or more pharmaceutically acceptable carriers.

[0118] In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant (*e.g.*, Freund's adjuvant (complete and incomplete)), excipient, or vehicle with which the therapeutic is administered.

[0119] Suitable pharmaceutically acceptable carriers include essentially chemically inert and nontoxic pharmaceutical compositions that do not interfere with the effectiveness of the biological activity of the pharmaceutical composition. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk,

glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc.

[0120] Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (*e.g.*, Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

[0121] Suitable forms of microcrystalline cellulose include, for example, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, and AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA, U.S.A.). An exemplary suitable binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM.

[0122] Examples of suitable fillers for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder/filler in pharmaceutical compositions of the present invention is typically present in about 50 to about 99 weight percent of the pharmaceutical composition.

[0123] Disintegrants are used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Too much of a disintegrant will produce tablets which may disintegrate in the bottle. Too little may be insufficient for disintegration to occur and may thus alter the rate and extent of release of the active ingredient(s) from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the active ingredient(s) should be used to form the dosage forms of the compounds disclosed herein. The amount of disintegrant used varies based upon the type of formulation and mode of administration, and is readily discernible to those of ordinary skill in the art. Typically, about 0.5 to about 15

weight percent of disintegrant, preferably about 1 to about 5 weight percent of disintegrant, can be used in the pharmaceutical composition.

[0124] Disintegrants that can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums or mixtures thereof.

[0125] Lubricants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, or mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, Texas), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, Mass), or mixtures thereof. A lubricant can optionally be added, typically in an amount of less than about 1 weight percent of the pharmaceutical composition.

[0126] Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a prophylactically or therapeutically effective amount of a hetero-substituted benzimidazole compound of the invention, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration. For example, oral administration requires enteric coatings to protect the hetero-substituted benzimidazole compound(s) from degradation within the gastrointestinal tract. In another example, the compound(s) may be administered in a liposomal formulation to shield the compound from degradative enzymes, facilitate transport, and effect delivery across cell membranes to intracellular sites.

[0127] In another embodiment, a pharmaceutical composition comprises a compound of the invention and/or one or more other therapeutic agents; and a pharmaceutically acceptable carrier. In a particular embodiment, the pharmaceutical composition comprises a compound of the invention, an antiviral, anti-inflammatory, anti-parasitic, anti-cancer or antibiotic agents, and a pharmaceutically acceptable carrier.

[0128] In one embodiment, a pharmaceutical composition, comprising a compound of the invention, with or without other therapeutic agents; and a pharmaceutically acceptable carrier, is at an effective dose.

[0129] Selection of the preferred effective dose can be determined (*e.g.,* via clinical trials) by a skilled artisan based upon the consideration of several factors which will be known to one of ordinary skill in the art. Such factors include the particular hetero-substituted benzimidazole compound, the compound's pharmacokinetic parameters such as bioavailability, metabolism, half-life, etc., which is established during the development procedures typically employed in obtaining regulatory approval of a pharmaceutical compound. Further factors in considering the dose include the disease to be treated, the benefit to be achieved in a patient, the patient's body mass, the patient's immune status, the route of administration, whether administration of the hetero-substituted benzimidazole compound is acute or chronic, concomitant medications, and other factors known by the skilled artisan to affect the efficacy of administered pharmaceutical agents.

[0130] Pharmaceutical compositions can be used in the preparation of unit dosage forms. Examples of dosage forms include, but are not limited to: tablets, caplets, capsules, such as soft elastic gelatin capsules, cachets, troches, lozenges, dispersions, suppositories, ointments cataplasms (poultices), pastes, powders, dressings, creams, plasters, solutions, patches, aerosols (*e.g.*, nasal sprays or inhalers), gels, liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (*e.g.,* aqueous or non-aqueous liquid suspensions, oil -in-water emulsions, or a water-in-oil emulsions), solutions, and elixers, liquid dosage forms suitable for parenteral administration to a subject; and sterile solids (*e.g.*, crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a subject.

[0131] In one embodiment, the pharmaceutical composition comprises a compound of the invention at a unit dose of about 1.0 mg and a pharmaceutically acceptable carrier. A recommended dose of a hetero-substituted benzimidazole compound of the invention is from about 1 mg to about 500 mg, more preferably from about 100 mg to about 400 mg, and even more preferably from about 200 mg to about 300 mg. For example, each tablet, cachet, or capsule contains from about 1 mg to about 500 mg, preferably from about 100 mg to about 400 mg , and more preferably from about 100 mg to about 300 mg of a hetero-substituted benzimidazole.

[0132] As other examples of dosage forms, suitable dosage forms for mucosal or transdermal routes include, but are not limited to, transdermal patches, ophthalmic solutions, sprays, and aerosols. A recommended dose of a hetero-substituted benzimidazole

compound of the invention can be administered as a spray or aerosol at 5 to 40 mg/ml, preferably 10 to 30 mg/ml, and most preferably 15 to 20 mg/ml. Transdermal compositions can also take the form of creams, lotions, and/or emulsions, which can be included in an appropriate adhesive for application to the skin or can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

[0133] A preferred transdermal dosage form is a "reservoir type" or "matrix type" patch, which is applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredient. For example, a preferred patch is worn for 24 hours and provides a total daily dose of from about 500 mg to about 2000 mg, more preferably from about 800 mg to about 1500 mg, and even more preferably from about 1000 mg to about 1300 mg per day. The patch can be replaced with a fresh patch when necessary to provide constant administration of the active ingredient to the patient.

[0134] In a preferred embodiment, the pharmaceutical compositions and dosage forms comprise a solid formulated for oral administration. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Pharmaceutical compositions of the invention suitable for oral administration can be presented as discrete dosage forms, such as capsules, cachets, or tablets, or aerosol sprays each containing a predetermined amount of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such dosage forms can be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient into association with the carrier, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

[0135] For example, a tablet can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient such as, but not limited to, a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[0136] In another preferred embodiment, the pharmaceutical compositions and dosage forms comprise aerosols suitable for pulmonary administration.

[0137] In other embodiments, the dosage form is a sterile, lyophilized powder suitable for reconstitution into a solution suitable for parenteral administration.

[0138] The actual amount of any particular compound of the invention administered can also depend on factors, such as, but not limited to, the type of viral infection, the toxicity of the compound to normal cells of the body, the rate of uptake of the compound by cells, the route of administration and the weight and age of the individual to whom the compound is administered. Because of the many factors present *in vivo* that may interfere with the action or biological activity of the compound, an effective amount of the compound may vary for each individual. Recommended daily doses can be given as a single once-a-day dose in the morning or as divided doses throughout the day.

[0139] Another embodiment of the invention encompasses a lactose-free pharmaceutical composition which comprises one or more compounds of the invention or a pharmaceutically acceptable prodrug, salt, solvate, or clathrate thereof and a pharmaceutically acceptable excipient. In a preferred embodiment the excipient is croscarmellose sodium, microcrystalline cellulose, pre-gelatinized starch, or magnesium stearate. In another preferred embodiment, the pharmaceutical compositions and dosage forms comprise a substantially free of mono- or di-saccharides.

[0140] In addition to the common dosage forms set out above, a hetero-substituted benzimidazole of the invention can also be administered by controlled release means or delivery devices that are well known to those of ordinary skill in the art, such as those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, the disclosures of which are incorporated herein by reference. These dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, or microspheres or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the pharmaceutical compositions of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

[0141] All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Advantages of controlled-release formulations include: 1) extended activity of the drug; 2)

reduced dosage frequency; and 3) increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and thus can affect the occurrence of side effects.

[0142] Most controlled-release formulations are designed to a drug to maintain a therapeutic effect over an extended period of time. Controlled-release of an active ingredient can be stimulated by various inducers, including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

[0143] Lactose-free compositions of the invention can comprise excipients which are well known in the art and are listed in the USP (XXI)/NF (XVI), which is incorporated herein by reference. In general, lactose-free compositions comprise an active ingredient, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Preferred lactose-free dosage forms comprise an active ingredient, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

[0144] This invention further encompasses anhydrous pharmaceutical compositions and dosage forms comprising an active ingredient, since water can facilitate the degradation of some compounds. For example, the addition of water (*e.g.*, 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. *See, e.g.*, Jens T. Carstensen, *Drug Stability: Principles & Practice*, 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate decomposition. Thus the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

[0145] An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

[0146] In this regard, the invention encompasses a method of preparing a solid pharmaceutical formulation comprising an active ingredient which method comprises admixing under anhydrous or low moisture/humidity conditions the active ingredient and an excipient (*e.g.*, lactose), wherein the ingredients are substantially free of water. The method can further comprise packaging the anhydrous or non-hygroscopic solid formulation under low moisture conditions. By using such conditions, the risk of contact with water is

reduced and the degradation of the active ingredient can be prevented or substantially reduced.

[0147] The invention also provides that a hetero-substituted benzimidazole compound of the invention is packaged in a hermetically sealed container such as an ampoule or sachette indicating the quantity of hetero-substituted benzimidazole compound. In one embodiment, the hetero-substituted benzimidazole compound is supplied as a dry sterilized lyophilized powder or water free concentrate in a hermetically sealed container and can be reconstituted, *e.g.*, with water or saline to the appropriate concentration for administration to a subject. In an alternative embodiment, an hetero-substituted benzimidazole compound or derivative thereof is supplied in liquid form in a hermetically sealed container indicating the quantity and concentration of the hetero-substituted benzimidazole compound or hetero-substituted benzimidazole compound derivative.

4.6 Combination Therapies

[0148] In certain embodiments of the present invention, the compounds and compositions of the invention can be used in combination therapy with at least one other therapeutic agent. The compound of the invention and the therapeutic agent can act additively or, more preferably, synergistically. In a preferred embodiment, a compound or a composition comprising a compound of the invention is administered concurrently with the administration of another therapeutic agent that can be part of the same composition as the compound of the invention or a different composition. In another embodiment, a compound or a composition comprising a compound of the invention is administered prior or subsequent to administration of another therapeutic agent.

[0149] The present compounds and compositions can be administered together with an anti-inflammatory agent. Useful anti-inflammatory agents include, but are not limited to, non-steroidal anti-inflammatory drugs such as salicylic acid, acetylsalicylic acid, methyl salicylate, diflunisal, salsalate, olsalazine, sulfasalazine, acetaminophen, indomethacin, sulindac, etodolac, mefenamic acid, meclofenamate sodium, tolmetin, ketorolac, dichlofenac, ibuprofen, naproxen, naproxen sodium, fenoprofen, ketoprofen, flurbinprofen, oxaprozin, piroxicam, meloxicam, ampiroxicam, droxicam, pivoxicam, tenoxicam, nabumetome, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, apazone and nimesulide; leukotriene antagonists including, but not limited to, zileuton, aurothioglucose, gold sodium thiomalate and auranofin; and other anti-inflammatory agents including, but not limited to, colchicine, allopurinol, probenecid, sulfinpyrazone and benzbromarone.

[0150] In other embodiments the compounds and compositions of the invention can be administered with another antiviral agent. Useful antiviral agents include, but are not

limited to, nucleoside analogs, such as zidovudine, acyclovir, gangcyclovir, vidarabine, idoxuridine, trifluridine, and ribavirin, as well as foscarnet, amantadine, rimantadine, saquinavir, indinavir, ritonavir, and the alpha-interferons. Such additional antiviral agents which may be used with a compound of the invention include, but are not limited to, those which function on a different target molecule involved in viral replication, e.g., those which act on a different target molecule involved in viral transmission; those which act on a different loci of the same molecule; and those which prevent or reduce the occurrence of viral resistance. One skilled in the art would know of a wide variety of antiviral therapies which exhibit the above modes of activity.

[0151] In a preferred embodiment of the invention, the novel antiviral compounds of the present invention are used in combination with therapies known in the art, useful for treating or preventing RSV infection. By example and not by limitation, one or more compounds of the invention can be used advantageously in combination with anti-RSV agents such as, nucleoside analogs such as Ribavarin, monoclonal antibodies such as Synagis® and antisense oligonucleotides or other small molecule inhibitors of RSV.

[0152] In order to evaluate potential therapeutic efficacy of the hetero-substituted benzimidazole compounds of the invention in combination with the antiviral therapeutics described above, these combinations may be tested for antiviral activity according to methods known in the art.

[0153] In other preferred embodiments, the novel antiviral compounds of the present invention are used in combination with supportive care, including administration of humidified oxygen and respiratory assistance.

4.7 Kits

[0154] The invention provides a pharmaceutical pack or kit comprising one or more containers filled with hetero-substituted benzimidazole compound useful for the treatment, prevention, or amelioration of symptoms associated with RSV infection. In other embodiments, the invention provides a pharmaceutical pack or kit comprising one or more containers filled with hetero-substituted benzimidazole compound useful for the treatment, prevention, or amelioration of symptoms associated with RSV infection, HPIV infection, hMPV infection or influenza.

[0155] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of

pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

5. BIOLOGICAL ASSAYS FOR THE CHARACTERIZATION AND DEMONSTRATION OF ANTIVIRAL ACTIVITY

[0156] The hetero-substituted benzimidazole compounds of the invention can also be assayed for their ability to inhibit or downregulate RSV replication using techniques known to those of skill in the art. For example, RSV replication can be assayed by a plaque assay such as described, *e.g.*, by Johnson et al., 1997, *Journal of Infectious Diseases* 176:1215-1224. The hetero-substituted benzimidazole compounds of the invention can also be assayed for their ability to inhibit or downregulate the expression of RSV polypeptides. Techniques known to those of skill in the art, including, but not limited to, Western blot analysis, Northern blot analysis, and room temperature-PCR can be used to measure the expression of RSV polypeptides. Further, the hetero-substituted benzimidazole compounds of the invention can be assayed for their ability to prevent the formation of syncytia.

[0157] The hetero-substituted benzimidazole compounds of the invention are preferably tested *in vitro*, and then *in vivo* for the desired therapeutic or prophylactic activity, prior to use in humans. For example, *in vitro* assays which can be used to determine whether administration of a specific hetero-substituted benzimidazole compound or composition of the present invention is indicated, include *in vitro* cell culture assays in which a subject tissue sample is grown in culture, and exposed to or otherwise administered a hetero-substituted benzimidazole compound or composition of the present invention, and the effect of such a hetero-substituted benzimidazole compound or composition of the present invention upon the tissue sample is observed. In various specific embodiments, *in vitro* assays can be carried out with representative cells of cell types involved in a RSV infection (*e.g.*, respiratory epithelial cells), to determine if a hetero-substituted benzimidazole compound or composition of the present invention has a desired effect upon such cell types. Preferably, the hetero-substituted benzimidazole compounds or compositions of the invention are also tested in *in vitro* assays and animal model systems prior to administration to humans. In a specific embodiment, cotton rats are administered a hetero-substituted benzimidazole compound of the invention or a composition of the invention, challenged with 10^5 pfu of RSV, and four or more days later the rats are sacrificed and RSV titer is determined. Further, in accordance with this embodiment, the tissues (*e.g.*, the lung tissues) from the sacrificed rats can be examined for histological changes.

[0158] In accordance with the invention, clinical trials with human subjects need not be performed in order to demonstrate the prophylactic and/or therapeutic efficacy of hetero-substituted benzimidazole compounds of the invention. *In vitro* and animal model studies using the hetero-substituted benzimidazole compounds or fragments thereof can be extrapolated to humans and are sufficient for demonstrating the prophylactic and/or therapeutic utility of said hetero-substituted benzimidazole compounds or hetero-substituted benzimidazole compound derivatives.

[0159] Hetero-substituted benzimidazole compounds or compositions of the present invention for use in therapy can be tested for their toxicity in suitable animal model systems, including but not limited to rats, mice, cows, monkeys, and rabbits. For *in vivo* testing of an hetero-substituted benzimidazole compound or composition's toxicity any animal model system known in the art may be used.

[0160] Efficacy in treating or preventing viral infection may be demonstrated by detecting the ability of a hetero-substituted benzimidazole compound or composition of the invention to inhibit the replication of the virus, to inhibit transmission or prevent the virus from establishing itself in its host, to reduce the incidence of RSV infection, or to prevent, ameliorate or alleviate one or more symptoms associated with RSV infection. The treatment is considered therapeutic if there is, for example, a reduction is viral load, amelioration of one or more symptoms, a reduction in the duration of a RSV infection, or a decrease in mortality and/or morbidity following administration of an hetero-substituted benzimidazole compound or composition of the invention.

[0161] The ability of the hetero-substituted benzimidazole compounds of the invention or fragments to block RSV-induced fusion after viral attachment to the cells is determined in a fusion inhibition assay.

[0162] Hetero-substituted benzimidazoles may be tested for antiviral activity against RSV by a variety of methods known in the art. A common method is to test for the hetero-substituted benzimidazole's effect on Hep2 cells, acutely infected with RSV, ability to fuse and cause syncytial formation on a monolayer of an infected line of cells (Hep2). The lower the observed level of fusion, the greater the antiviral effect of the hetero-substituted benzimidazole is determined to be.

5.1 Assays for Membrane Fusion Activity

[0163] Assays for cell fusion events are well known to those of skill in the art, and may be used in conjunction with the compounds of the invention to test the compounds' antifusogenic capabilities.

[0164] Cell fusion assays are generally performed *in vitro* and are known in the art to correlate with *in vivo* activity including in humans. Such an assay may comprise culturing cells which, in the absence of any treatment would undergo an observable level of syncytial formation. For example, uninfected cells may be incubated in the presence of cells chronically infected with a virus that induces cell fusion. Such viruses may include, but are not limited to paramyxoviruses such as influenza virus, HPIV, hMPV and in particular, RSV.

[0165] For the assay, cells are incubated in the presence of a compound to be assayed. For each compound, a range of compound concentrations may be tested. This range should include a control culture wherein no compound has been added.

[0166] Standard conditions for culturing cells, well known to those of ordinary skill in the art, are used. After incubation for an appropriate period (24 hours at 37°C, for example) the culture is examined microscopically for the presence of multinucleated giant cells, which are indicative of cell fusion and syncytial formation. Well known stains, such as crystal violet stain, may be used to facilitate the visualization of syncytial formation.

5.2 Assays for Membrane Antiviral Activity

[0167] The antiviral activity exhibited by the compounds of the invention may be measured, for example, by easily performed *in vitro* assays, such as those described below, which can test the compounds' ability to inhibit syncytia formation, or their ability to inhibit infection by cell-free virus. Using these assays, such parameters as the relative antiviral activity of the compounds, exhibit against a given strain of virus and/or the strain specific inhibitory activity of the compound can be determined.

[0168] A cell fusion assay may be utilized to test the compounds' ability to inhibit viral-induced, such as RSV-induced, syncytia formation *in vitro*. Such an assay may comprise culturing uninfected cells in the presence of cells chronically infected with a syncytial-inducing virus and a compound to be assayed. For each compound, a range of compound concentrations may be tested. This range should include a control culture wherein no compound has been added. Standard conditions for culturing, well known to those of ordinary skill in the art, are used. After incubation for an appropriate period (24 hours at 37°C, for example) the culture is examined microscopically for the presence of multinucleated giant cells, which are indicative of cell fusion and syncytia formation. Well known stains, such as crystal violet stain, may be used to facilitate syncytial visualization.

[0169] Standard methods which are well-known to those of skill in the art may be utilized for assaying non-retroviral activity. See, for example, Pringle *et al.* (Pringle *et al.*, 1985, *J. Medical Virology* 17:377-386) for a discussion of respiratory syncytial virus and

parainfluenza virus activity assay techniques. Further, see, for example, "Zinsser Microbiology", 1988, Joklik, W.K. *et al.*, eds., Appleton & Lange, Norwalk, CT, 19th ed., for a general review of such techniques. These references are incorporated by reference herein in their entirety.

[0170] Additionally, anti-RSV activity can be assayed *in vivo* via well known mouse models that are standard models of human injection. For example, RSV can be administered intranasally to mice of various inbred strains. Virus replicates in lungs of all strains, but the highest titers are obtained in P/N, C57L/N and DBA/2N mice. Infection of BALB/c mice produces an asymptomatic bronchiolitis characterized by lymphocytic infiltrates and pulmonary virus titers of 10^4 to 10^5 pfu/g of lung tissue (Taylor *et al.*, 1984, *Infect. Immun.* 43:649-655).

[0171] Cotton rat models of RSV are also well known (see, *e.g.*, Johnson *et al.*, 1999, *Journal of Infectious Diseases* 180:35-40; Prince *et al.*, 1985, *J. Virol.* 55:517-520). Virus replicates to high titer in the nose and lungs of the cotton rat but produces few if any signs of inflammation.

5.3 Test Results of Compounds

[0172] The assay utilized herein tested the ability of the hetero-substituted benzimidazole compounds of the invention to selectively disrupt the ability of Hep2 cell monolayers acutely infected with RSV (*i.e.*, cells which are infected with a multiplicity of infection of greater than 2) to fuse and cause syncytial formation. The lower the observed level of fusion, the greater the antiviral activity of the compound was determined to be.

[0173] Uninfected confluent monolayers (seeded at 2.2 x 10^4 cells/well) of Hep2 cells were grown in microtiter wells (96-well plates) in EMEM (Eagle Minimum Essential Medium w/o L-glutamine [Bio Whittaker Cat. No. 12-125F] with 3% fetal bovine serum (FBS; which had been heat inactivated for 30 minutes at 56°C; Bio Whittaker Cat. No. 14-501F), antibiotics (penicillin/streptomycin; Bio Whittaker Cat. No. 17-602E) added at 1%, and glutamine added at 1% (complete EMEM). The plates were incubated for 24 hours and used for antiviral assays and cytotoxicity assays.

[0174] To prepare Hep2 cells for addition to uninfected cells, cultures of acutely infected Hep2 cells were washed with DPBS (Dulbecco's Phosphate Buffered Saline w/o calcium or magnesium; Bio Whittaker Cat. No. 17-512F) and cell monolayers were removed with Versene (1:5000; Gibco Life Technologies Cat. No. 15040-017). The cells were spun for 10 minutes and resuspended in 3% FBS. Cell counts were performed using a hemacytometer. Persistent cells were added to the uninfected Hep2 cells.

[0175] The antiviral assay was conducted by first removing all medium from the wells containing uninfected Hep2 cells, adding 100 µl complete EMEM, then adding hetero-substituted benzimidazole compounds (eight 3-fold dilutions with 20 µM concentration as the highest final concentration) in 50 µl complete EMEM. Approximately 50 syncitial plaque forming units (PFU) of RSV in 50 µl was added per well and the plates were incubated in a CO_2 incubator at 37°C for 48 hours. Each plate contained uninfected control wells and infected untreated control wells for calculation of % inhibition (EC_{50}) for each concentration.

[0176] After incubation, cells in control wells were checked for fusion centers, medium was removed from the wells followed by addition to each well of either Crystal Violet stain or XTT. With respect to Crystal Violet, approximately 50µl 0.25% Crystal Violet stain in methanol was added to each well. The wells were rinsed immediately, to remove excess stain, and were allowed to dry. The number of syncytia per well were then counted, using a dissecting microscope.

[0177] With respect to XTT (2,3-bis[2-methoxy-4-nitro-5-sulfophenyl]-2H-tetrazolium-5-carboxyanilide inner salt), 50µl XTT (1mg/ml in RPMI buffered with 100 mM HEPES, pH 7.2-7.4, plus 5% DMSO) were added to each well. The $OD_{450/690}$ was measured (after blanking against growth medium without cells or reagents, and against reagents) according to standard procedures.

[0178] For antiviral assays at 48 hours post infection, cells in control wells were checked for syncytial plaques. Medium was removed from the wells followed by addition of approximately 50 µl Crystal Violet stain (0.25% Crystal Violet, 0.25% Giemsa dissolved in 10% formaldehyde, 70% methanol, and 20% H_2O). The wells were incubated at room temperature for 5 minutes, rinsed with H_2O to remove excess stain, and allowed to dry. The number of syncytia per well were counted using a dissecting microscope. The 50% inhibitory concentration (EC_{50}) for each compound was calculated from the dose response curve.

[0179] Cytotoxicity assays were conducted by first removing all medium from the well containing uninfected Hep2 cells, adding 100 µl complete EMEM, and then adding hetero-substituted benzimidazole compounds (eight 3-fold dilutions with 100 µM concentration as the highest final concentration). Complete EMEM (50 µl) was added to each well instead of virus and the plates were incubated in a CO_2 incubator at 37°C for 48 hours.

[0180] At 48 hours, the cytotoxicity assays were developed by adding to each well 50µl of XTT (1 mg/ml in PBS) containing 0.01-0.02 mM of the electron coupling agent

phenazine methosulfate (PMS). The plates were incubated for 2-4 hours at 37°C and then read in a 96-well plate reader at 450 nm. Plotting the % average OD of treated wells compared to the cell control vs. compound concentration generated dose response curves. CC_{50} (50% inhibitory cytotoxic concentration) values for each compound were then calculated from these curves.

5.3.1 Results

[0181] The compounds listed in Tables 1-2 have been screened for inhibitory activity against RSV. The IC_{50} (50% cell inhibitor concentration) and the CC_{50} (50% inhibitory cytotoxic concentration) results are displayed in columns 4 and 5 of table 1 and columns 3 and 4 of table 2 above.

6. EXAMPLES

[0182] Certain embodiments of the invention are illustrated by the following non-limiting examples.

6.1 Synthesis of Hetero-substituted benzimidazole Compounds

Nucleophilic aromatic halide displacement:

[0183] To a single neck flask equipped with a condenser and under nitrogen atmosphere was charged 2-Chloro-3-nitropyridine (25g, 0.158 mole), Aminomethylbenzimidazole hydrochloride (36.5g, 0.166 mole) and 200 ml of Ethanol. To this slurry was charged diisopropylethyl amine (137 ml, 0.790 mole) and heated to 65 degrees celcius for 1 hour. Tlc in 5%methanol/ Methylene Chloride (product Rf; 0.5). The reaction was concentrated under vacuo to 100 ml and then cool in an ice bath. Filtered solid and washed cake with minimal amount of Methyl ethyl Ketone to give (1H-Benzoimidazol-2-ylmethyl)-(3-nitro-pyridin-2-yl)-amine, a canary Yellow solid (wt= 15.76 g)

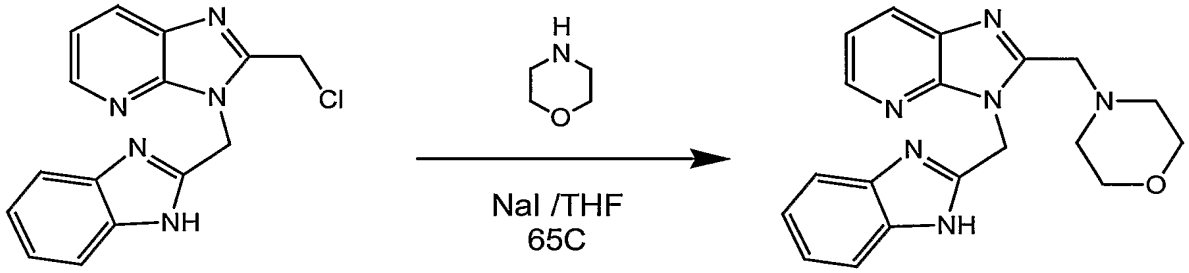
Reduction of Nitro compound:

[0184] To a Parr reaction vessel was charged (1H-Benzoimidazol-2-ylmethyl)-(3-nitro-pyridin-2-yl)-amine (1.0 g, .0037 mole) and 50 ml of methanol. Then add 400 mg of Palladium on charcoal 10% by weight and subject to 60 PSI of Hydrogen for 8 hours. Reaction removed from hydrogenator, filtered through a bed of celite and anhydrous magnesium sulfate. The celite bed was washed 2 times with 15 ml of methanol. Concentrate the methanol to give N^2-(1H-Benzoimidazol-2-ylmethyl)-pyridine-2,3-diamine as a tan solid (yield 70%).

Conversion to Benzimidazole-deazapurine methyl chloride:

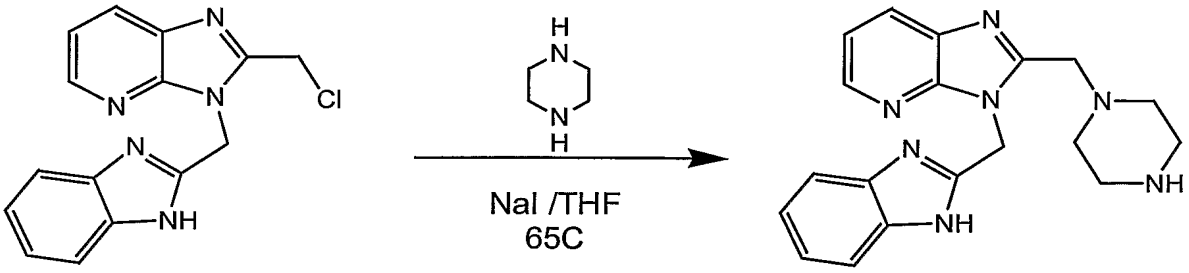
[0185] To a flask under nitrogen was charged N^2-(1H-Benzoimidazol-2-ylmethyl)-pyridine-2,3-diamine (1.8 g, 7.5 mMole) and methyl-chloro ethyl imidate (3.68 g, 23mMole) and 200 ml methanol and the reaction allowed to stir at 65 degree celcius for 12 hours. The reaction was allowed to cool and then concentrated to a solid. The solid was purified using 5% methanol/ Methylene Chloride. Combined fractions with product and concentrate to give the 3-(1H-Benzoimidazol-2-ylmethyl)-2-chloromethyl-3H-imidazo[4,5-b]pyridine as a solid. (yield 50%).

6.1.1 Synthesis of 3-(1H-Benzoimidazol-2-ylmethyl)-2-morpholin-4-ylmethyl-3H-imidazo[4,5-b]pyridine



[0186] Benzimidazole-deazapurine methyl chloride (0.223 g, 0.75 mmol) and NaI (.022 g, 0.15 mmol) were dissolved in 10 ml dry THF in a 25 ml round bottom flask. Morpholine (0.144 g, 1.65 mmol) was added and the reaction was stirred magnetically under nitrogen at 65C in an oil bath for 3 hours. The reaction was evaporated under vacuum. The resulting material was acidified with trifluoroacetic acid and purified by reverse phase HPLC.

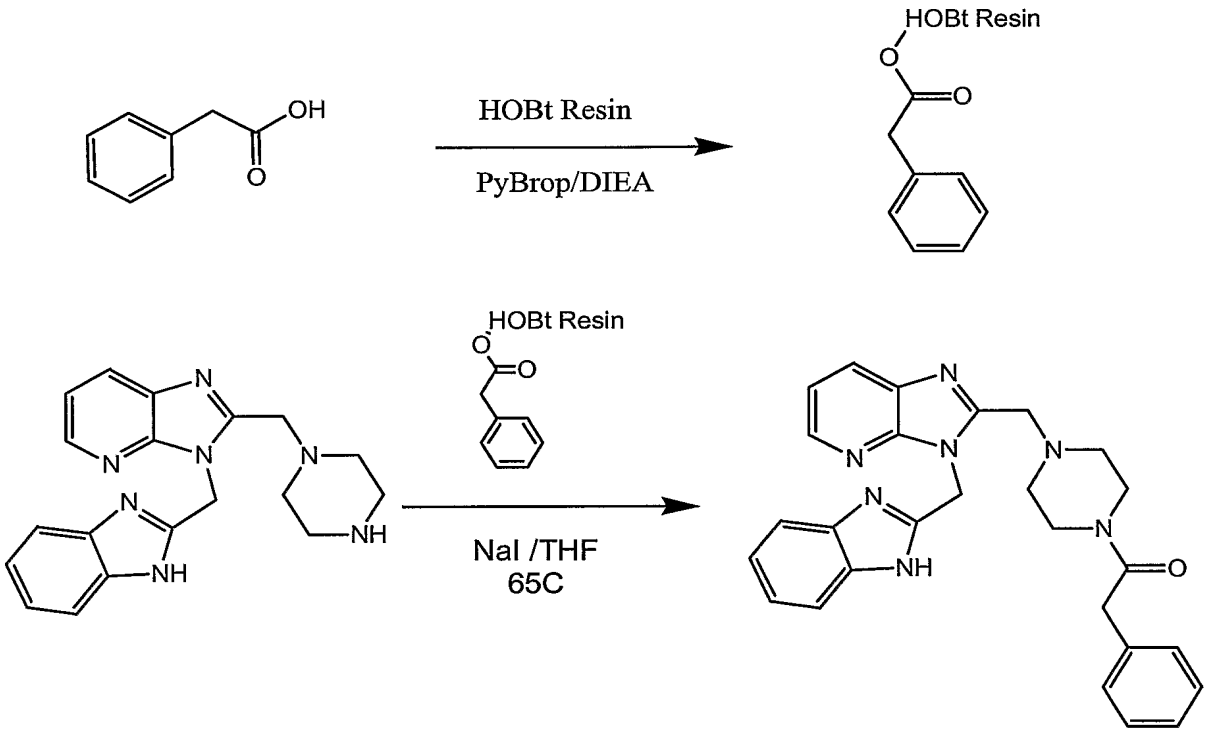
6.1.2 Synthesis of 3-(1H-Benzoimidazol-2-ylmethyl)-2-piperazin-1-ylmethyl-3H-imidazo[4,5-b]pyridine



[0187] Benzimidazole-deazapurine methyl chloride (0.298 g, 1.0 mmol) and NaI (.022 g, 0.15 mmol) were dissolved in 15 ml dry THF in a 25 ml round bottom flask.

Piperazine (0.190 g, 2.2 mmol) was added and the reaction was stirred magnetically under nitrogen at 65C in an oil bath for 3 hours. The reaction was evaporated under vacuum. The resulting material was acidified with trifluoroacetic acid and purified by reverse phase HPLC.

6.1.3 Synthesis of 1-{4-[3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylmethyl]-piperazin-1-yl}-2-phenyl-ethanone



[0188] HOBt resin (Argonaut 2 g, 0.84 mmol/g, 1.68 mmol total) was swelled in DMF 15 minutes. After draining, phenylacetic acid (0.46 g, 3.36 mmol) and PyBrop (1.57 g, 3.36 mmol) were dissolved in 10 ml DMF. DIEA (1.1 ml, 6.7 mmol) was added to this solution. After 1 minute the solution was added to the resin. The resin slurry was shaken 2 hours, the washed and dried.

[0189] Benzimidazole-deazapurine methyl piperazine (0.079 g, 0.23 mmol) was dissolved in 2 ml DCM. This was added to the phenylacetyl-HOBt resin and shaken. After 1 hour, 50 uL DIEA was added. After 2 hours the solution was filtered from the resin and evaporated. The product was acidified with trifluoroacetic acid and purified by reverse phase HPLC.

6.1.4 General Procedure for the Synthesis of 3-(1H-Benzoimidazol-2-ylmethyl)-2-(4-R-sulfonyl-piperazin-1-ylmethyl)-3H-imidazo[4,5-b]pyridine

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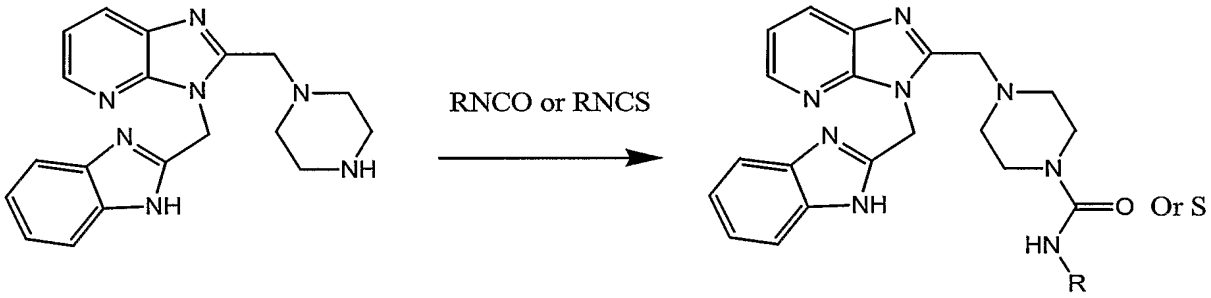
[0190] Benzimidazole-deazapurine methyl piperazine (0.035 g per sample, 0.10 mmol) was dissolved in anhydrous THF (5 ml per sample). This solution was pipetted in equal portions to 20 ml glass scintillation vials. To each vial was added sulfonyl chloride (0.10 mmol) and DIEA (0.066 ml per sample, 0.4 mmol) and the capped vials were shaken at room temperature for 3 hours. The samples were evaporated in a GeneVac DD4 vacuum centrifuge. The resulting materials were acidified with trifluoroacetic acid and purified by reverse phase HPLC on a 1" C18 column. The resulting fractions were combined and lyophilized.

6.1.5 General Procedure for the Synthesis of 4-[3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo [4,5-b]pyridin-2-ylmethyl]-piperazine-1-carboxylic acid R-amide or 4-[3-(1H-Benzoimidazol-2-ylmethyl)-3H-imidazo [4,5-b]pyridin-2-ylmethyl]-piperazine-1-carbothiic acid R-amide



[0191] Benzimidazole-deazapurine methyl piperazine (0.052 g per sample, 0.15 mmol) was dissolved in anhydrous THF (5 ml per sample). This solution was pipetted in equal portions to 20 ml glass scintillation vials. To each vial was added isocyanate or isothiocyanate (0.15 mmol) and DIEA (0.049 ml per sample, 0.3 mmol) and the capped vials were shaken in a dry heat block at 50C for 3 days. The samples were evaporated in a GeneVac DD4 vacuum centrifuge. The resulting materials were acidified with trifluoroacetic acid and purified by reverse phase HPLC on a 1" C18 column. The resulting fractions were combined and lyophilized.

Equivalents

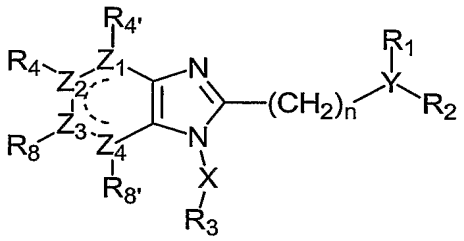
[0192] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

[0193] All publications, patents and patent applications mentioned in this specification are herein incorporated by reference into the specification to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference.

THE CLAIMS

WHAT IS CLAIMED IS:

1. A compound of the Formula I:



Formula I

or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein:

Z_1, Z_2, Z_3 and Z_4 are each independently nitrogen or carbon and at least one of Z_1, Z_2, Z_3 and Z_4 is carbon;

R_1 and R_2 are each independently: hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted arylalkyl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, thioaryl, or R_1 and R_2 may be joined to form a substituted or unsubstituted ring including a heterocycloalkyl, heterocycloaryl or heteroaryl group;

R_3 is hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl; wherein, if present the substiuent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino

acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl;

R_4, $R_{4'}$, R_8, and $R_{8'}$ are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl; wherein, if present the substituent is at least one alkanoyl, imide, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl;

X is a bond, straight chain or branched substituted or unsubstituted alkyl, -(alkyl)N-, -(alkyl)O-, -C=N-, carbonyl, phosphorus, or sulfur;

Y is nitrogen, phosphorus, oxygen, or sulfur; wherein, if Y is oxygen or sulfur, R_2 is not present; and

n is an integer from 0 to about 4;

with the proviso that compounds of Formula I do not include a compound where R_1, R_2, R_3, R_4, $R_{4'}$, R_8, $R_{8'}$ are hydrogen, X is a bond, and n = 0 or 1; or a compound where R_3, R_4, $R_{4'}$, R_8, and $R_{8'}$ are hydrogen, X is a bond, n = 0, one of R_1 or R_2 is a hydrogen, and the other is a 4-piperidinyl or N-substituted 4-piperidinyl.

2. The compound according to claim 1, wherein:

R_1 and R_2 are each independently saturated or unsaturated straight or branched substituted or unsubstituted C_1-C_8 alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted4 to 12 membered heterocycloalkyl or heteroaryl group having at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is least one C_1-C_4 alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, ester, amine, or C_1-C_4 alkylamine;

R_3 is hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl C_1-C_8 alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted 4 to 12 membered heterocycloalkyl or heteroaryl having at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent, is at least one hydroxy, fluoride, chloride, bromine, C_1-C_4 alkoxy, C_1-C_4 sulfide, C_1-C_4 sulfonyl, nitro, carboxylic acid, ester, amine, or C_1-C_4 alkylamine;

R_4, $R_{4'}$, R_8, and $R_{8'}$ each independently is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, amine, C_1-C_4 alkylamine, carboxylic acid, ester, C_1-C_4 amide, halide, hydroxy, nitro, C_1-C_4 sulfide, C_1-C_4 sulfonyl, or sulfonamide;

X is a bond, straight chain or branched substituted or unsubstituted C_1-C_4 alkyl, -(C_1-C_4 alkyl)N-, -(C_1-C_4 alkyl)O-, carbonyl, or sulfur;

Y is nitrogen, phosphorus, oxygen, or sulfur; wherein, if Y is oxygen or sulfur, R_2 is not present; and

n is from 0 to about 1.

3. The compound according to claim 1, wherein:

X is a bond, methylene, or ethylene;

Y is nitrogen, phosphorus, oxygen, or sulfur; wherein, if Y is oxygen or sulfur, R_2 is not present; and

n is 1.

4. The compound according to claim 1, wherein:

R_3 is a substituted or unsubstituted phenyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted quinolinyl, substituted or unsubstituted acridinyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted benzodioxanyl, substituted or unsubstituted benzimidazolyl, substituted or unsubstituted phenylphenolyl, wherein, if present, the substituent is at least one C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 sulfide, C_1-C_4 sulfonyl, nitro, fluoride, chloride, or bromide;

X is a methylene;

Y is nitrogen, phosphorus, oxygen, or sulfur; wherein, if Y is oxygen or sulfur, R_2 is not present; and

n is 1.

5. The compound according to claim 1, wherein at least one of R_1, R_2, or R_3 is a benzimidazole.

6. The compound according to claim 5, wherein X is a bond or methylene, R_3 is a 2-benzimidazole, and at least one of R_1 or R_2 is a 2-benzimidazole or 2-methylenebenzimidazole.

7. The compound according to claim 1, wherein the compound of Formula I is an enantiomer or diastereomer.

8. The compound according to claim 1, wherein $R_{4'}$ and $R_{8'}$ are hydrogen, methyl, methyl ester, ethyl ester, C_1-C_2 amide, carboxylic acid, methoxy, or sulfonamide.

9. The compound according to claim 1, wherein $R_{4'}$ and $R_{8'}$ are both hydrogen.

10. The compound according to claim 1, wherein R_4, $R_{4'}$, R_8, and $R_{8'}$ are all hydrogen.

11. The compound according to claim 1, wherein at least one of R_4, $R_{4'}$, R_8, or $R_{8'}$ is not hydrogen.

12. The compound according to claim 1, wherein at least two of R_4, $R_{4'}$, R_8, and $R_{8'}$ are not hydrogen.

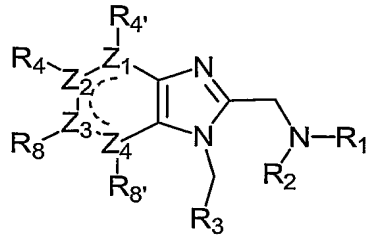
13. The compound according to claim 1, wherein at least three of R_4, $R_{4'}$, R_8, and $R_{8'}$ are not hydrogen.

14. The compound according to claim 1, wherein at least one of Z_2 and Z_4 is nitrogen.

15. The compound according to claim 1, wherein both of Z_2 and Z_4 are nitrogen.

16. The compound according to claim 1, wherein Z_4 is nitrogen.

17. A compound of the Formula II:



Formula II

or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein:

Z_1, Z_2, Z_3 and Z_4 are each independently nitrogen or carbon and at least one of Z_1, Z_2, Z_3 and Z_4 is carbon;

R_1 and R_2 are each independently: hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted arylalkyl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, thioaryl, or R_1 and R_2 may be joined to form a substituted or unsubstituted ring including a heterocycloalkyl, heterocycloaryl or heteroaryl group;

R_3 is hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl; wherein, if present the substiuent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, amine, amide, alkylamine, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl;

R_4, $R_{4'}$, R_8, and $R_{8'}$ are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl; wherein, if present the substituent is at least one alkyl, hydroxy, halide, methoxy, ethoxy, amine, cyano. alkanoyl, imide, amine, amide, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, halogen, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl.

18. The compound according to claim 17, wherein

R_1 and R_2 are each independently: C_1-C_8 saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl,4 to 12 membered heterocycloalkyl or heteroaryl with at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is at least one hydroxy, halide, methoxy, ethoxy, carboxylic acid, ester, amine, or alkylamine.

19. The compound according to claim 16, wherein

R_3 is C_1-C_4 straight chain or branched alkyl, substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 5 to 12 membered aryl, substituted or unsubstituted 5 to 12 membered arylalkyl, or 4 to 12 membered heterocycloalkyl or heteroaryl with at least one oxygen, sulfur, or nitrogen atom within the ring, wherein, if present, the substituent is at least one hydroxy, halide, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 sulfide, C_1-C_4 sulfonyl, nitro, carboxylic acid, ester, amine, or C_1-C_4 alkylamine.

20. The compound according to claim 17, wherein

R_4, $R_{4'}$, R_8, and $R_{8'}$ are each independently hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, amine, C_1-C_4 alkylamine, C_1-C_4 amide, carboxylic acid, ester, halide, hydroxy, nitro, C_1-C_4 sulfide, C_1-C_4 sulfonyl, or sulfonamide.

21. The compound according to claim 17, wherein at least one of R_1, R_2, or R_3 is a benzimidazole.

22. The compound according to claim 17, wherein R_3 is a 2-benzimidazole, and at least one of R_1 or R_2 is a 2-benzimidazole or 2-methylene benzimidazole.

23. The compound according to claim 17, wherein the compound of Formula II is an enantiomer or diastereomer.

24. The compound according to claim 17, wherein R_4, $R_{4'}$, R_8, and $R_{8'}$ are hydrogen.

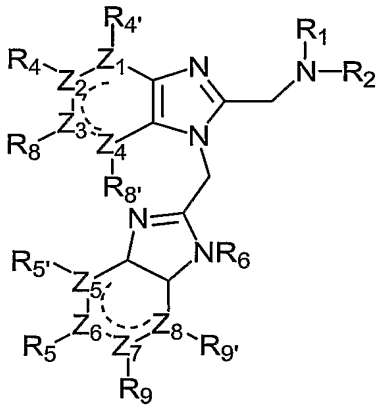
25. The compound according to claim 17, wherein at least one of R_4, $R_{4'}$, R_8, or $R_{8'}$ is not hydrogen.

26. The compound according to claim 17, wherein at least one of Z_2 and Z_4 is nitrogen.

27. The compound according to claim 17, wherein both of Z_2 and Z_4 are nitrogen.

28. The compound according to claim 17, wherein Z_4 is nitrogen.

29. A compound of the Formula III:



Formula III

or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein:

Z_1, Z_2, Z_3 and Z_4 are each independently nitrogen or carbon and at least one of Z_1, Z_2, Z_3 and Z_4 is carbon;

Z_5, Z_6, Z_7 and Z_8 are each independently nitrogen or carbon;

R_1 and R_2 are each independently: hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl, substituted or unsubstituted heteroaryl, alkanoyl, or imide, wherein, if present, the substituent is at least one alkyl, alkanoyl, imide, alkoxy, carboxylic acid, amine, amide, alkylamine, cyano, halide, hydroxy, nitro, thiol, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl;

R_4, $R_{4'}$, R_5, $R_{5'}$, R_8, $R_{8'}$, R_9, and $R_{9'}$ are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, alkylamine, amide, carboxylic acid, ester, nitro, sulfide, sulfonyl, sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; and

R_6 is hydrogen, saturated or unsaturated,saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, nitro, thiol, alkanoyl, imide, acetal, acetylene, aminal, amino acid, azo, diazo, carbamate, carboalkoxy ester,

cyanohydrin, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, ketone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, sulfone, or sulfonic acid.

30. The compound according to claim 29, wherein:

R_1, and R_2 are each independently saturated or unsaturated straight or branched substituted or unsubstituted C_1-C_{11} alkyl, C_1-C_{12} alkoxy, substituted or unsubstituted C_1-C_{11} alkylamino, substituted or unsubstituted 3 to 10 membered cycloalkyl, substituted or unsubstituted 3 to 10 membered heterocycloalkyl, substituted or unsubstituted 5 to 12 membered aryl, substituted or unsubstituted 5 to 12 membered arylalkyl, substituted or unsubstituted 4 to 13 membered heteroaryl, alkanoyl, or imide, wherein, if present, the substituent is at least one C_1-C_4 alkyl, cyano, fluoride, chloride, bromide, hydroxy, nitro, or thiol.

31. The compound according to claim 29, wherein:

R_4, $R_{4'}$, R_5, $R_{5'}$, R_8, $R_{8'}$, R_9, and $R_{9'}$ are each independently hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, amine, C_1-C_4 alkylamine, C_1-C_4 amide, carboxylic acid, ester, halide, hydroxy, nitro, C_1-C_4 sulfide, C_1-C_4 sulfonyl, or sulfonamide.

32. The compound according to claim 29, wherein:

R_6 is a saturated or unsaturated straight or branched substituted or unsubstituted C_1-C_8 alkyl, C_1-C_4 alkoxy, substituted or unsubstituted C_2-C_6 alkylamino, substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 4 to 5 membered heterocycloalkyl having at least one oxygen, nitrogen, or sulfur atom within the ring, substituted or unsubstituted 5 to 16 membered aryl, substituted or unsubstituted 5 to 10 membered arylalkyl, substituted or unsubstituted 4 to 6 membered heteroaryl having at least one oxygen, nitrogen, or sulfur atom in the ring, C_1-C_4 alkanoyl, or imide, wherein, if present, the substituent is at least one C_1-C_4 alkyl, cyano, fluoride, chloride, bromide, hydroxy, nitro, or thiol.

33. The compound according to claim 29, wherein:

R_1 and R_2 are each independently hydrogen, methyl, ethyl, propyl, isopropyl, sec-butyl, 3-methylbutyl, 2-methyl-2-propenyl, 2-propynyl, pentyl, hexyl, 2-butylyl, 2-hydroxy-2-(4-hydroxyphenyl)ethyl, 2-(2-pyridinyl)ethyl, 2-hydroxy-2-(3,4-dihydroxyphenyl)ethyl, 3-pyridinylmethyl, 2,5-difluorobenzyl, 4-trifluoromethoxyphenylmethyl, 3-methoxypropyl, 2-hydroxyethyl, 4-phenylbutyl, 2-phosphonatethyl, 3-(2-methyl)ethoxypropyl, 2-(2-

thiophenyl)ethyl, N-benzyl-4-piperidinyl, 3-(1-pyrrolidinyl)propyl, 2-(N,N-diethyl)ethyl, tetrahydrofuranylmethyl, cyclopentyl, or cyclohexyl.

34. The compound according to claim 29, wherein R_6 is hydrogen.

35. The compound according to claim 29, wherein the compound of Formula III is an enantiomer or diastereomer.

36. The compound according to claim 29, wherein $R_{4'}$, $R_{5'}$,$R_{8'}$, and $R_{9'}$ are hydrogen.

37. The compound according to claim 29, wherein at least one of R_4, $R_{4'}$, R_8, and $R_{8'}$ is not hydrogen.

38. The compound according to claim 29, wherein at least two of R_4, $R_{4'}$, R_8, and $R_{8'}$ are not hydrogen.

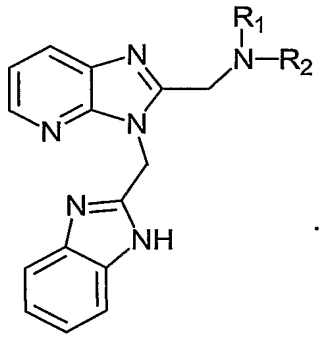
39. The compound according to claim 29, wherein at least one of R_5, $R_{5'}$, R_9, and $R_{9'}$ is not hydrogen.

40. The compound according to claim 29, wherein at least one of Z_2 and Z_4 is nitrogen.

41. The compound according to claim 29, wherein both of Z_2 and Z_4 are nitrogen.

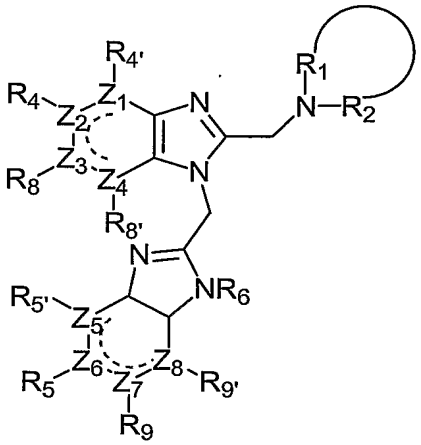
42. The compound according to claim 29, wherein Z_4 is nitrogen.

43. The compound according to claim 29 having Formula V:



Formula V

44. A compound of the Formula IV:



Formula IV

or a pharmaceutically-acceptable prodrug, salt, solvate, hydrate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomer thereof, wherein:

Z_1, Z_2, Z_3 and Z_4 are each independently nitrogen or carbon and at least one of Z_1, Z_2, Z_3 and Z_4 is carbon;

Z_5, Z_6, Z_7 and Z_8 are each independently nitrogen or carbon;

$-R_1-N-R_2-$ form a saturated or unsaturated substituted or unsubstituted heterocycloalkyl ring, substituted or unsubstituted heteroaryl ring, wherein, if present, the substituent is at least one substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkoxy, amides, sulfonamides, esters, hydroxy, halide, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, carbonyl, nitro, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl;

R_4, $R_{4'}$, R_5, $R_{5'}$, R_6, R_8, $R_{8'}$, R_9, and $R_{9'}$ are each independently hydrogen, halide, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, amine, alkylamine, amide,

carboxylic acid, ester, nitro, sulfide, sulfonyl, or sulfonamide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl; and

R_6 is hydrogen, saturated or unsaturated straight or branched substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloaryl or substituted or unsubstituted heteroaryl; wherein, if present, the substituent is at least one alkanoyl, imide, alkyl, hydroxy, halide, methoxy, ethoxy, carboxylic acid, cyano, nitro, alkanoyl, imide, acetal, acetylene, aminal, amino acid, amino acid ester, azo, diazo, azide, carbamate, carboxylic acid ester, carboalkoxy ester, cyanohydrin, diazonium salt, glucoside, glucuronide, halocarbon, polyhalocarbon, halocarbonoxy, polyhalocarbonoxy, hydroxylamine, ketone, lactone, nitrile, nitrile oxide, N-oxides, nucleoside linked, oxime, phosphate, phosphinate, phosphonate, phosphonic acid, quaternary ammonium salt, sulfoxide, sulfone, sulfonate ester, sulfinate ester, sulfonic acid, thioacetal, thiocarboxylic acid, thiol, or thioaryl.

45. The compound according to claim 44, wherein:

$-R_1-N-R_2-$ form a saturated or unsaturated, substituted or unsubstituted 3 to 7 membered cycloalkyl, substituted or unsubstituted 3 to 7 membered heterocycloalkyl, substituted or unsubstituted 3 to 7 membered heteroaryl, wherein, if present, the substituent is at least one substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 alkoxy, C_1-C_4 esters, hydroxy, fluoride, chloride, bromide, substituted or unsubstituted 3 to 8 membered aryl, substituted or unsubstituted 4 to 6 membered cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, carbonyl, or nitro.

46. The compound according to claim 44, wherein:

R_4, $R_{4'}$, R_5, $R_{5'}$, R_6, R_8, $R_{8'}$, R_9, and $R_{9'}$ are each independently hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, amine, C_1-C_4 alkylamine, C_1-C_4 amide, carboxylic acid, ester, halide, hydroxy, nitro, C_1-C_4 sulfide, C_1-C_4 sulfonyl, or sulfonamide.

47. The compound according to claim 44, wherein $R_{4'}$, $R_{5'}$, $R_{8'}$, and $R_{9'}$ are hydrogen.

48. The compound according to claim 44 wherein at least one of R_4, $R_{4'}$, R_8, and $R_{8'}$ is not hydrogen.

49. The compound according to claim 44, wherein R_5, $R_{5'}$, R_9, and $R_{9'}$ are hydrogen.

50. The compound according to claim 44, wherein at least one of R_5, $R_{5'}$, R_9, and $R_{9'}$ is not hydrogen.

51. The compound according to claim 44, wherein R_6 is hydrogen.

52. The compound according to claim 44, wherein:

$-R_1-N-R_2-$ form a 5, 6, or 8 membered ring; and

R_4, $R_{4'}$, R_5, $R_{5'}$, R_6, R_8, $R_{8'}$, R_9, and R_9 are each independently are hydrogen C_1-C_2 alkyl, C_1-C_2 alkoxy, amine, C_1-C_2 alkylamine, fluoride, chloride, bromide, hydroxy, nitro, C_1-C_2 sulfide, or C_1-C_2 sulfonyl.

53. The compound according to claim 44, wherein the 5, 6, or 8 membered ring formed by $-R_1-N-R_2-$ is a pyrrolidinyl, piperidinyl, pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, piperazinyl, quinolinyl, acridinyl, thiazole, morpholinyl, or unsubstituted or substituted phenyl wherein, if present, the substituent, if present, is at least one methyl, ethyl, ester, methanol, 2-ethanol, or aldehyde.

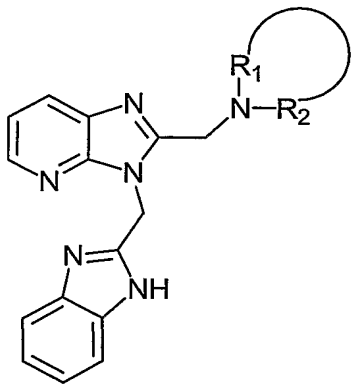
54. The compound according to claim 44, wherein the compound of Formula IV is an enantiomer or diastereomer.

55. The compound according to claim 44, wherein at least one of Z_2 and Z_4 is nitrogen.

56. The compound according to claim 44, wherein both of Z_2 and Z_4 are nitrogen.

57. The compound according to claim 44, wherein Z_4 is nitrogen.

58. The compound according to claim 44 having Formula VI:



Formula VI

59. A pharmaceutical composition comprising the compound according to claim 1 and a pharmaceutically acceptable carrier.

60. A pharmaceutical composition comprising the compound according to claim 17 and a pharmaceutically acceptable carrier.

61. A pharmaceutical composition comprising the compound according to claim 29 and a pharmaceutically acceptable carrier.

62. A pharmaceutical composition comprising the compound according to claim 43 and a pharmaceutically acceptable carrier.

63. A pharmaceutical composition comprising the compound according to claim 44 and a pharmaceutically acceptable carrier.

64. A pharmaceutical composition comprising the compound according to claim 58 and a pharmaceutically acceptable carrier.

65. A method of treating, preventing, or ameliorating one or more symptoms associated with a respiratory syncytial virus (RSV) infection in a mammal comprising administering to the mammal a therapeutically or prophylactically effective amount of the compound of claim 1, 17, 29, 43, 44 or 58 and a pharmaceutically acceptable carrier.

66. The method of treating, preventing, or ameliorating a viral infection according to claim 65, wherein the compound is administered orally, parenterally, transdermally, or mucosally.

67. The method of treating, preventing, or ameliorating a viral infection according to claim 65, wherein the compound is administered in an amount from about 10 mg/kg/day to about 15 mg/kg/day.

68. The method of treating, preventing, or ameliorating a viral infection according to claim 65, wherein the mammal is a human subject.

69. The method of treating, preventing, or ameliorating a viral infection according to claim 68, wherein the human subject is a human infant.

70. A method of inhibiting membrane fusion associated events characteristic of a viral infection in a mammal comprising administering the compound of claim 1, 17, 29, 43, 44 or 58 and a pharmaceutically acceptable carrier.

71. A method of treating, preventing, or ameliorating one or more symptoms associated with a HPIV infection in a mammal comprising administering to the mammal a therapeutically or prophylactically effective amount of the compound of claim 1, 17, 29, 43, 44 or 58 and a pharmaceutically acceptable carrier.

72. A method of treating, preventing, or ameliorating one or more symptoms associated with a hMPV infection in a mammal comprising administering to the mammal a therapeutically or prophylactically effective amount of the compound of claim 1, 17, 29, 43, 44 or 58 and a pharmaceutically acceptable carrier.

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(54) Title: ALKYLAMINOACETAMIDE LUBRICANT ADDITIVES

(57) Abstract: The invention relates to a composition comprising a base oil of lubricating viscosity and alkylamine, alkylenedi-, alkylenetri- or alkylenetetra-amine derivatives of N-alkyl-halo-acetamides. These compounds are useful as ashless, phosphorus-free and sulfur-free anti-wear and friction modifying additives for lubricating oils.

Alkylaminoacetamide Lubricant Additives

The invention relates to the use of alkylaminoacetamides, that is alkylamine, alkylenedi-, alkylenetri- or alkylenetetra-amine derivatives of N-alkyl-halo-acetamides, as ashless, phosphorus-free and sulfur-free antiwear and friction modifying additives for lubricating oils.

U.S. Patent Specification Nos. 5,282,872 and *5,071,445* disclose amide, amide/ammonium salt or ammonium salt compounds of an aminoalkylene polycarboxylic acid and a secondary fatty amine as additives in fuels.

U.S. Patent Specification No. 5,376,155 teaches the reaction products of aminoalkylenecarboxylic acids with primary or secondary amines as paraffin dispersants in mineral oils.

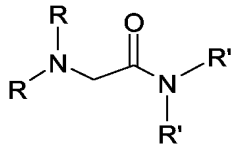
It has now been found that certain N-alkylaminoacetamide or alkylenedi-, alkylenetri- or alkylenetetra-amine acetamide compounds are excellent antiwear and friction modifying additives for lubricating oils.

The invention relates to a composition, which comprises

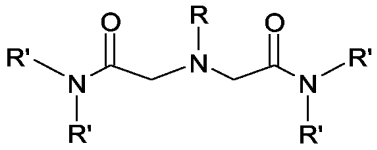
a) A base oil of lubricating viscosity, and

b) An effective antiwear or friction modifying amount of at least one compound selected from the group consisting of

N-alkylaminoacetamide compounds (I), (II):

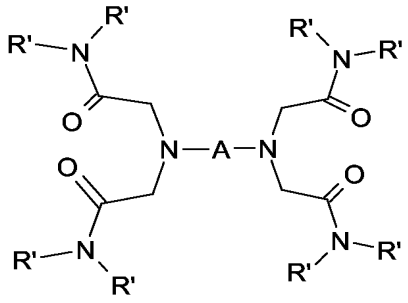


(I),



(II) and

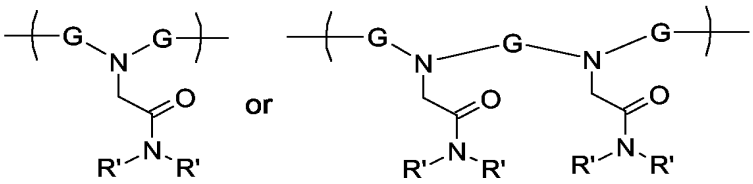
Alkylenedi-, alkylenetri- or alkylenetetra-amine acetamide compounds (III):



(III),

Wherein

A is alkylene of from 2 to 6 carbon atoms or is a group



,

G, each independently, is alkylene of 2 to 6 carbon atoms,

R, each independently, is alkyl or alkenyl of 1 to 8 carbon atoms and

R', each independently, is hydrogen or alkyl or alkenyl or 1 to 24 carbon atoms,

provided that

each amide nitrogen atom is either mono- or disubstituted by alkyl or alkenyl; and that the alkyl or alkenyl groups have 8 to 24 carbon atoms, if the amide nitrogen is monosubstituted by alkyl or alkenyl; and

that the carbon atoms of the alkyl or alkenyl groups have 8 to 18 carbon atoms, if the amide nitrogen is disubstituted by alkyl or alkenyl. Claim 1

According to specific embodiment of the invention, the compounds (I), (II) or (III) are present from about 0.15% to about 10% by weight, based on the weight of the lubricant.

Component a)

A base oil of lubricating viscosity ("lubricant") can be used for the preparation of combustion engine oils. The total sulphur content in the low sulphur oil should not exceed the limit of more than 0.3 weight% with regard to the total weight of the composition.

Suitable combustion engine oils are based, for example, on mineral oils, natural oils, synthetic oils or mixtures thereof. These oils are known and familiar to the person skilled in the art and are described in standard reference books, such as in *Chemistry and Technology of Lubricants; Mortier, R.M. and Orszulik, S.T. (Editors); 1992 Blackie and Son Ltd. for GB, VCH-Publishers N.Y. for U.S., ISBN 0-216-92921-0, pages 208 et seq. and 269 et seq.; in Kirk-Othmer Encyclopedia of Chemical Technology, Fourth Edition 1969, J. Wiley & Sons, New York, Vol. 13, page 533 et seq. (Hydraulic Fluids); Performance Testing of Hydraulic Fluids; R. Tourret and E.P. Wright, Hyden & Son Ltd. GB, on behalf of The Institute of Petroleum London, ISBN 0 85501 317 6; Ullmann's Encyclopedia of Ind. Chem., Fifth Completely Revised Edition, Verlag Chemie, DE-Weinheim, VCH-Publishers for U.S., Vol. A 15, page 423 et seq. (lubricants), Vol. A 13, page 165 et seq. (hydraulic fluids)*.

The base oil of lubricating viscosity is preferably a mineral oil derived lubricating base oil that contains 80% by mass or more of a saturated hydrocarbon component. Various methods for producing the mineral oil derived lubricating base oil are available. For example, the lubricating base oil may be a paraffin oil or a naphthenic oil obtainable by subjecting a lubricating oil fraction derived from an atmospheric or vacuum distillation of crude oil to refining processes such as deasphalting, solvent refining such as solvent extraction with furfural, hydrocracking, solvent or catalytic dewaxing, such as solvent or catalytic dewaxing, hydrotreating, such as hydrocracking or hydrofinishing, clay treatment, such as washing with acid treated or activated clay, or chemical refining such as washing with caustic soda or sulphuric acid and the like. Combinations of these methods are also available for producing the mineral oil derived lubricating base oil.

Component b)

According to a preferred embodiment, the invention relates to a composition, which comprises at least one compound selected from the group consisting of N-alkylaminoacetamide compounds (I) and (II), wherein the total number of carbon atoms of the alkyl or alkenyl groups are from 14 to 18 carbon atoms if the amide nitrogen is disubstituted by alkyl or alkenyl. Claim 2

According to another preferred embodiment, the invention relates to a composition, which comprises at least one compound selected from the group consisting of alkylenedi-, alkylenetri- and alkylenetetra-amine acetamide compounds (III), wherein A and G are selected from the group consisting of ethylene, propylene, hexamethylene and 2-methylpentylene. Claim 3

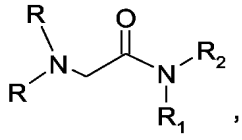
According to other preferred embodiments, the invention relates to compositions, wherein each R' is independently straight or branched chain alkyl or alkenyl of 7 to 9 carbon atoms claim 4; or

wherein one R' is hydrogen and the other one is straight or branched chain alkyl or alkenyl of 14 to 18 carbon atoms Claim 5; or

where each R' is identical and is straight or branched chain alkyl or alkenyl of 7 to 9 carbon atoms Claim 6.

For example, if an amide nitrogen is disubstituted by alkyl or alkenyl, the total carbon atoms of said alkyls or alkenyls combined are from 14 to 18 carbon atoms.

A particularly preferred embodiment relates to a composition, wherein the compounds (I), (II) and (III) are selected from the group consisting of



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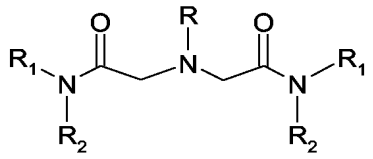

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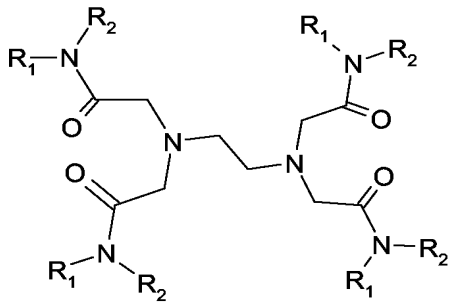

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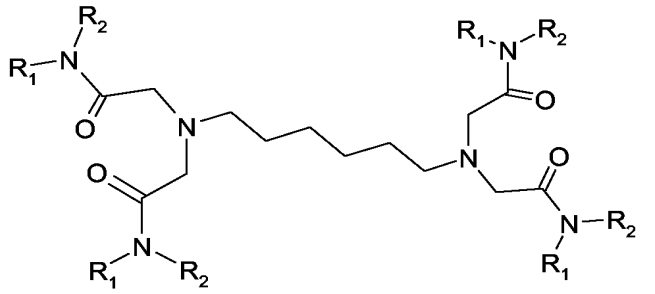

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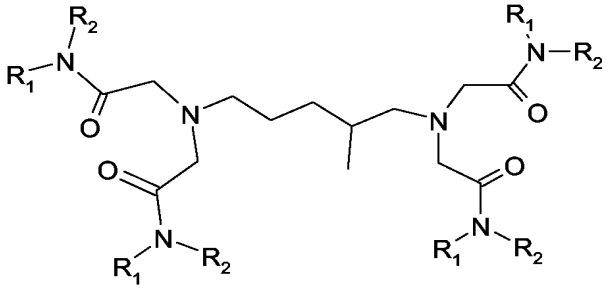
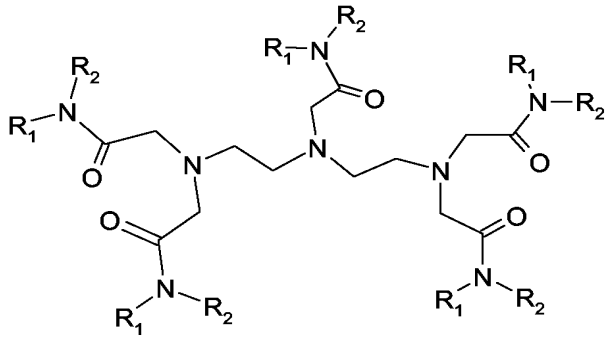


and



wherein R is n-octyl and each of R_1 and R_2 are 2-ethylhexyl or n-octyl or one of R_1 and R_2 is hydrogen and the other is oleyl, n-octyl, t-octyl or dodecyl. Claim 7

A further embodiment relates to novel alkylaminoacetamide compounds (I)

(I)

Wherein

R, each independently, is alkyl or alkenyl of 1 to 8 carbon atoms and

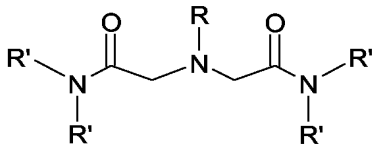
R', each independently, is hydrogen or alkyl or alkenyl or 1 to 24 carbon atoms,

provided that

each amide nitrogen atom is either mono- or disubstituted by alkyl or alkenyl; and that the alkyl or alkenyl groups have 8 to 24 carbon atoms, if the amide nitrogen is monosubstituted by alkyl or alkenyl; and

that the alkyl or alkenyl groups have 8 to 18 carbon atoms, if the amide nitrogen is disubstituted by alkyl or alkenyl. Claim 8

Another embodiment relates to novel N-alkylaminoacetamide compounds (II)



(II)

Wherein

R, each independently, is alkyl or alkenyl of 1 to 8 carbon atoms and

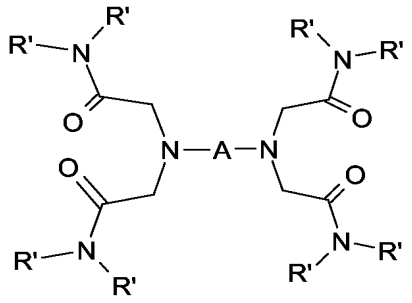
R', each independently, is hydrogen or alkyl or alkenyl or 1 to 24 carbon atoms,

provided that

each amide nitrogen atom is either mono- or disubstituted by alkyl or alkenyl; and that the alkyl or alkenyl groups have 8 to 24 carbon atoms, if the amide nitrogen is monosubstituted by alkyl or alkenyl; and

that the alkyl or alkenyl groups have 8 to 18 carbon atoms, if the amide nitrogen is disubstituted by alkyl or alkenyl Claim 9 .

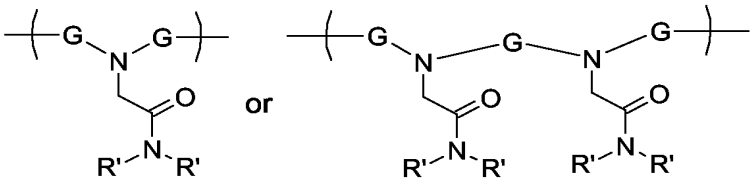
Another embodiment relates to novel alkylenedi-, alkylenetri- or alkylenetetra-amine acetamide compounds (III)



(III)

wherein

A is alkylene of from 2 to 6 carbon atoms or is a group

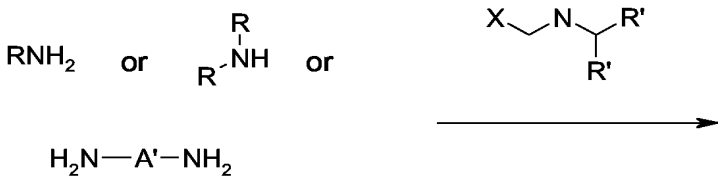


,

G, each independently, is alkylene of 2 to 6 carbon atoms,

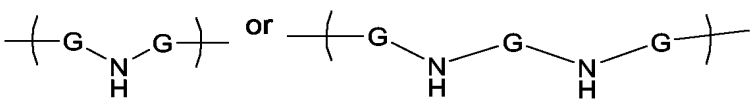
R', each independently, is alkyl or alkenyl of 1 to 24 carbon atoms, where for each amide group, the total number of carbon atoms of the alkyls or alkenyl groups are from 14 to 18 carbon atoms. Claim 10

The present N-alkylaminoacetamide compounds and alkylenedi-, alkylenetri- or alkylene-tetra-amine acetamide compounds are prepared for example by alkylation of primary or secondary amines with mono- or di-alkyl substituted halo-acetamides according to the following sheme:



where

A' is alkylene of from 2 to 6 carbon atoms or is a group



,

X is Cl, Br or I and R, R' and G are as previously defined.

Chloroacetamides are described in for example *U.S. Patent Specification. Nos. 2,746,901* and *4,801,618*. The compounds (I) and (II) may be prepared according to methods disclosed in these references. Haloacetamides are also described by *van Esch, et al., J. Org. Chem. 1995, 60, 1599-1610*, and by *Weaver, et al., J. Am. Chem. Soc. 1947, 69, 515-516*.

The compounds (I), (II) and (III) are prepared by reacting a haloacetamide with an appropriate amine or di-, tri- or tetra-amine in the ratio of about 1 molar equivalent of haloacetamide per reactive aminic hydrogen. For example, butylamine has two reactive aminic hydrogen atoms, dibutylamine has one reactive aminic hydrogen, and ethylenediamine has four reactive aminic hydrogen atoms. The reagents are mixed neat or in a suitable solvent, at a suitable temperature and for a suitable time to complete the reaction. The reagents are mixed in the presence of an inorganic base, for example sodium carbonate.

Presumably, the compounds prepared in this way are not salts. They do not contain any ammonium salts. They do not contain any ammonium carboxylate salts, which would exist if prepared for example from the reaction of an alkylamine and an aminoalkylcarboxylic acid.

In the additives (I), (II) or (III), R is for example alkyl or alkenyl of 5 to 8 carbon atoms. A and G are, for example, ethylene, propylene, hexamethylene or 2-methylpentylene. For example, each amide is disubstituted by alkyl or alkenyl. For example, each R' is the same. For example, each R' is straight or branched chain alkyl or alkenyl of 7 to 9 carbon atoms. For example, one R' of each amide is hydrogen and the other is straight or branched chain alkyl or alkenyl of 14 to 18 carbon atoms.

For example, in the additives, each of the amide nitrogens are disubstituted by alkyl or alkenyl and the total carbon atoms of said alkyls or alkenyls for each amide combined are from 14 to 18 carbon atoms, that is to say, each R' is straight or branched chain alkyl or alkenyl of 7 to 9 carbon atoms.

For instance, in the additives, R is n-octyl and each R' is 2-ethylhexyl or n-octyl or one R' of each amide is hydrogen and the other is oleyl, n-octyl, t-octyl or dodecyl.

Alkyl is straight or branched chain and is for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, 2-ethylbutyl, n-pentyl, isopentyl, 1-methylpentyl, 1,3-dimethylbutyl, n-hexyl, 1-methylhexyl, n-heptyl, isoheptyl, 1,1,3,3-tetramethylbutyl, 1-methylheptyl, 3-methylheptyl, n-octyl, 2-ethylhexyl, 1,1,3-trimethylhexyl, 1,1,3,3-tetramethylpentyl, nonyl, decyl, undecyl, 1-methylundecyl, dodecyl, 1,1,3,3,5,5-hexamethylhexyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, icosyl or docosyl.

Alkenyl is also straight or branched and is an ethylenically unsaturated version of alkyl, for example allyl, oleyl, docosenyl, and the like.

Alkylene is straight or branched and is for example ethylene, propylene, methylethylene, tetramethylene, pentamethylene or hexamethylene.

Suitable amines are for example octylamine, dioctylamine, butylamine, dibutylamine, ethylenediamine, diethylenetriamine, dipropylenetriamine, H_2N-$(CH_2)_3NH(CH_2)_2NH(CH_2)_3NH_2$, and the like.

The additive compounds (I), (II) and (III), that is the additives, are highly soluble in the lubricant, for example are soluble at 1%, 2% or for example at 5% on a weight/weight basis at room temperature.

The additives, when employed in lubricants (lubricating oils) for internal combustion engines, serve both to reduce wear of the engine's moving parts and to reduce friction. The additives provide an economic method to accomplish desired antiwear and reduced friction properties without the use of a metal such as Zn, or the elements S or P, enabling a significant reduction or the elimination of P, S, and Zn containing additives.

The lubricants of component a) are, for example, those employed in internal combustion engines. The lubricants have necessary lubricating viscosity and are for example mineral oils or are synthetic and mixtures thereof.

Greases or other solid lubricants are also lubricating oils according to this invention.

Synthetic hydrocarbon oils include long chain alkanes such as cetanes and olefin polymers such as trimer and tetramers of octane and decene. These synthetic oils can be mixed with 1) ester oils such as pentaerythritol esters of monocarboxylic acids having about 2 to 20 carbon atoms, 2) polyglycol ethers, 3) polyacetals and 4) siloxane fluids. Useful among the synthetic esters are those made from polycarboxylic acids and monohydric alcohols. For example, ester fluids made from pentaerythritol or mixtures thereof with di- and tripentaerythritol, and an aliphatic monocarboxylic acid containing from 1 to 20 carbon atoms, or mixtures of such acids. Other examples are ester fluids made from trimethylolpropane and an aliphatic monocarboxylic acid containing from 1 to 20 carbon atoms, or mixtures of such acids.

The lubricating oils are also for example crude oil, industrial lubrication oils, cutting oil, metal working fluids and greases.

The additives of this invention are advantageously present in the lubricant at a level of for example from about 0.15% to about 10.0% by weight of lubricant. For example, the additives are present from about 0.15% to about 7.0%, from about 0.25% to about 5.0%, from about 0.5% to about 3.0%, or from about 0.75% to about 2.0% by weight of the lubricant. For ex-

ample, the additives are present from about 0.5% to about 5.0%, from about 0.5% to about 7.0%, or from about 0.5% to about 10.0% by weight, based on the weight of the lubricant.

In the vent that in lubricating compositions operated under extremely adverse conditions, such as lubricating compositions for marine diesel engines, that the additives of this invention may be present in amounts of up to about 30.0% by weight, or more, of the total weight of the lubricating composition.

The lubricating oils in accordance with the invention may additionally include other additives, which are added in order to improve still further the basic properties of these formulations; such additives include antioxidants, metal passivators, rust inhibitors, corrosion inhibitors, viscosity index improvers, extreme pressure agents, pour point depressants, solid lubricants, dispersants, detergents, antifoams, color stabilizers, further high-pressure additives, demulsifiers, antiwear additives and additives which reduce the coefficient of friction. Such additives are added in the customary amounts in each case in the range from in each case about 0.01% to 10.0% by weight, based on the lubricating oil.

The list below gives some representative examples of such additional additives:

Examples of antioxidants:

1) Alkylated monophenols, for example 2,6-di-tert-butyl-4-methylphenol, 2-butyl-4,6-dimethylphenol, 2,6-di-tert-butyl-4-ethylphenol, 2,6-di-tert-butyl-4-n-butylphenol, 2,6-di-tert-butyl-4-iso-butylphenol, 2,6-di-cyclopentyl-4-methylphenol, 2-(a-methyl-cyclohexyl)-4,6-dimethylphenol, 2,6-di-octadecyl-4-methylphenol, 2,4,6-tri-cyclo-hexylphenol, 2,6-di-tert-butyl-4-methoxymethylphenol, linear or sidechain-branched nonylphenols, for example 2,6-di-nonyl-4-methylphenol, 2,4-dimethyl-6-(1'-methyl-undec-1'-yl)phenol, 2,4-dimethyl-6-(1'-methylheptadec-1'-yl)phenol, 2,4-dimethyl-6-(1'-methyltridec-1'-yl)phenol or mixtures thereof;

2) Alkylthiomethylphenols, for example 2,4-di-octylthiomethyl-6-tert-butylphenol, 2,4-di-octylthiomethyl-6-methylphenol, 2,4-di-octylthiomethyl-6-ethylphenol or 2,6-di-dodecylthiomethyl-4-nonylphenol;

3) Hydroquinones and alkylated hydroquinones, for example 2,6-di-tert-butyl-4-methoxyphenol, 2,5-di-tert-butylhydroquinone, 2,5-di-tert-amylhydroquinone, 2,6-diphenyl-4-octadecyloxyphenol, 2,6-di-tert-butyl-hydroquinone, 2,5-di-tert-butyl-4-hydroxyanisole, 3,5-di-tert-butyl-4-hydroxyanisole, 3,5-di-tert-butyl-4-hydroxyphenyl stearate or bis(3,5-di-tert-butyl-4-hydroxyphenyl) adipate;

4) Tocopherols, for example α-, β-, γ- or δ-tocopherol or mixtures thereof (vitamin E);

5) Hydroxylated thiodiphenyl ethers, for example 2,2'-thiobis(6-tert-butyl-4-methylphenol), 2,2'-thiobis(4-octylphenol), 4,4'-thiobis(6-tert-butyl-3-methylphenol), 4,4'-thiobis-(6-tert-butyl-2-methylphenol), 4,4'-thiobis(3,6-di-sec-amylphenol) or 4,4'-bis(2,6-dimethyl-4-hydroxyphenyl) disulfide;

6) Alkylidenebisphenols, for example 2,2'-methylenebis(6-tert-butyl-4-methylphenol), 2,2'-methylenebis(6-tert-butyl-4-ethylphenol), 2,2'-methylenebis(4-methyl-6-(alpha-methylcyclohexyl)-phenol), 2,2'-methylenebis(4-methyl-6-cyclohexylphenol), 2,2'-methylenebis(6-nonyl-4-methylphenol), 2,2'-methylenebis(4,6-di-tert-butylphenol), 2,2'-ethylidenebis(4,6-di-tert-butylphenol), 2,2'-ethylidenebis(6-tert-butyl-4-isobutylphenol), 2,2'-methylenebis(6-(alpha-methylbenzyl)-4-nonylphenol), 2,2'-methylene-bis(6-(alpha,alpha-dimethylbenzyl)-4-nonylphenol), 4,4'-methylenebis(2,6-di-tert-butylphenol), 4,4'-methylenebis(6-tert-butyl-2-methylphenol), 1,1-bis(5-tert-butyl-4-hydroxy-2-methylphenyl)butane, 2,6-bis(3-tert-butyl-5-methyl-2-hydroxybenzyl)-4-methylphenol, 1,1,3-tris(5-tert-butyl-4-hydroxy-2-methylphenyl)butane, 1,1-bis(5-tert-butyl-4-hydroxy-2-methylphenyl)-3-n-dodecylmercaptobutane, ethylene glycol bis(3,3-bis(3'-tert-butyl-4'-hydroxyphenyl)butyrate), bis(3-tert-butyl-4-hydroxy-5-methylphenyl)dicyclo-pentadiene, bis(2-(3'-tert-butyl-2'-hydroxy-5'-methylbenzyl)-6-tert-butyl-4-methylphen yl)terephthalate, 1,1-bis(3,5-dimethyl-2-hydroxyphenyl)butane, 2,2-bis(3,5-di-tert-butyl-4-hydroxyphenyl)propane, 2,2-bis(5-tert-butyl-4-hydroxy-2-methylphenyl)-4-n-dodecylmercaptobutane or 1,1,5,5-tetra(5-tert-butyl-4-hydroxy-2-methylphenyl)-pentane;

7) O- N- and S-Benzyl compounds, for example 3,5,3',5'-tetra-tert-butyl-4,4'-dihydroxydibenzyl ether, octadecyl 4-hydroxy-3,5-dimethylbenzylmercaptoacetate, tridecyl 4-hydroxy-3,5-di-tert-butylbenzylmercaptoacetate, tris(3,5-di-tert-butyl)amine, bis(4-tert-butyl-3-hydroxy-2,6-dimethylbenzyl)dithioterephthalate, bis(3,5-di-tert-butyl-4-hydroxybenzyl) sulfide or isooctyl 3,5-di-tert-butyl-4-hydroxy-benzylmercaptoacetate;

8) Hydroxybenzylated malonates, for example-dioctadecyl 2,2-bis(3,5-di-tert-butyl-2-hydroxybenzyl)malonate, dioctadecyl 2-(3-tert-butyl-4-hydroxy-5-methylbenzyl)-malonate, didodecyl mercaptoethyl-2,2-bis(3,5-di-tert-butyl-4-hydroxybenzyl)-malonate or di(4-(1,1,3,3-tetramethylbutyl)phenyl)2,2-bis(3,5-di-tert-butyl-4-hydroxybenzyl)malonate;

9) Aromatic hydroxybenzyl compounds, for example 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-2,4,6-trimethylbenzene, 1,4-bis(3,5-di-tert-butyl-4-hydroxybenzyl)-2,3,5,6-tetramethylbenzene or 2,4,6-tris(3,5-di-tert-butyl-4-hydroxybenzyl)phenol;

10) Triazine compounds, for example 2,4-bisoctylmercapto-6-(3,5-di-tert-butyl-4-hydroxyanilino)-1,3,5-triazine, 2-octylmercapto-4,6-bis(3,5-di-tert-butyl-4-hydroxyanilino)-1,3,5-triaz-

ine, 2-octylmercapto-4,6-bis(3,5-di-tert-butyl-4-hydroxyphenoxy)-1,3,5-triazine, 2,4,6-tris(3,5-di-tert-butyl-4-hydroxyphenoxy)-1,2,3-triazine, 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-isocyanurate, 1,3,5-tris(4-tert-butyl-3-hydroxy-2,6-dimethylbenzyl) isocyanurate, 2,4,6-tris(3,5-di-tert-butyl-4-hydroxyphenylethyl)-1,3,5-triazine, 1,3,5-tris(3,5-di-tert-butyl-4-hydroxyphenylpropionyl)hexahydro-1,3,5-triazine or 1,3,5-tris(3,5-dicyclohexyl-4-hydroxybenzyl)-isocyanurate;

11) Benzylphosphonates, for example dimethyl 2,5-di-tert-butyl-4-hydroxybenzyl-phosphonate, diethyl 3,5-di-tert-butyl-4-hydroxybenzylphosphonate, dioctadecyl 3,5-di-tert-butyl-4-hydroxybenzylphosphonate, dioctadecyl 5-tert-butyl-4-hydroxy-3-methylbenzylphosphonate or the calcium salt of the monoethyl ester of 3,5-di-tert-butyl-4-hydroxybenzylphosphonic acid;

12) Acylaminophenols, for example 4-hydroxylauranilide, 4-hydroxystearanilide or octyl N-(3,5-di-tert-butyl-4-hydroxyphenyl)carbamate;

13) Esters of β-(3,5-di-tert-butyl-4-hydroxyphenyl)propionic acid, β-(5-tert-butyl-4-hydroxy-3-methylphenyl)propionic acid, β-(3,5-dicyclohexyl-4-hydroxyphenyl)-propionic acid, 3,5-di-tert-butyl-4-hydroxyphenylacetic acid or β-(5-tert-butyl-4-hydroxyphenyl)-3-thiabutyric acid with mono- or polyhydric alcohols, e.g. with methanol, ethanol, n-octanol, i-octanol, octadecanol, 1,6-hexanediol, 1,9-nonanediol, ethylene glycol, 1,2-propanediol, neopentyl glycol, thiodiethylene glycol, diethylene glycol, triethylene glycol, pentaerythritol, tris(hydroxyethyl) isocyanurate, N,N'-bis(hydroxyethyl)oxalamide, 3-thiaundecanol, 3-thiapentadecanol, trimethyl-hexanediol, trimethylolpropane, 4-hydroxymethyl-1-phospha-2,6,7-trioxabicyclo(2.2.2)octane, glycerol or transesterification products based on natural triglycerides of, for example, coconut oil, rape seed oil, sunflower oil or colza oil;

14) Amides of β-(3,5-di-tert-butyl-4-hydroxyphenyl)propionic acid, e.g. N,N'-bis(3,5-di-tert-butyl-4-hydroxyphenylpropionyl)hexamethylenediamine, N,N'-bis(3,5-di-tert-butyl-4-hydroxyphenylpropionyl)trimethylenediamine or N,N'-bis(3,5-di-tert-butyl-4-hydroxyphenylpropionyl)hydrazine;

15) Ascorbic acid (vitamin C);

16) Amine-type antioxidants, for example N,N'-diisopropyl-p-phenylenediamine, N,N'-di-sec-butyl-p-phenylenediamine, N,N'-bis(1,4-dimethylpentyl)-p-phenylenediamine, N,N'-bis(1-ethyl-3-methyl-pentyl)-p-phenylenediamine, N,N'-bis(1-methyl-heptyl)-p-phenylendiamine, N,N'-dicyclohexyl-p-phenylenediamine, N,N'-diphenyl-p-phenylenediamine, N,N'-di-(naphth-2-yl)-p-phenylenediamine, N-isopropyl-N'-phenyl-p-phenylenediamine, N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine, N-(1-methylheptyl)-N'-phenyl-p-phen-

ylenediamine, N-cyclohexyl-N'-phenyl-p-phenylenediamine, 4-(p-toluenesulfonamido)-diphenylamine, N, N'-dimethyl-N,N'-di-sec-butyl-p-phenylenediamine, diphenylamine, N-allyldiphenylamine, 4-isopropoxy-diphenylamine, N-phenyl-1-naphthylamine, N-(4-tert-octylphenyl)-1-naphthylamine, N-phenyl-2-naphthylamine, octylated diphenylamine, e.g. p,p'-di-tert-octyldiphenyl-amine, 4-n-butylaminophenol, 4-butyrylamino-phenol, 4-nonanoylamino-phenol, 4-dodecanoylaminophenol, 4-octadecanoylamino-phenol, di-(4-methoxyphenyl)-amine, 2,6-di-tert-butyl-4-dimethylamino-methyl-phenol, 2,4'-diamino-diphenylmethane, 4,4'-diamino-diphenylmethane, N,N,N',N'-tetramethyl-4,4'-diamino-diphenylmethane, 1,2-di-((2-methyl-phenyl)-amino)-ethane, 1,2-di-(phenylamino)propane, (o-tolyl)biguanide, di(4-(1',3'-dimethyl-butyl)-phenyl)amine, tert-octylated N-phenyl-1-naphthylamine, a mixture of mono- and dialkylated tert-butyl/tert-octyldiphenylamines, a mixture of mono- and dialkylated nonyldiphenylamines, a mixture of mono- and dialkylated dodecyldiphenylamines, a mixture of mono- and dialkylated isopropyl/isohexyldiphenylamines, mixtures of mono- and dialkylated tert-butyldiphenylamines, 2,3-dihydro-3,3-dimethyl-4H-1,4-benzothiazine, phenothiazine, a mixture of mono- and dialkylated tert-butyl/tert-octyl-phenothiazines, a mixture of mono- and dialkylated tert-octyl-phenothiazines, N-allylphenothiazine, N,N,N',N'-tetraphenyl-1,4-diaminobut-2-ene, N,N-bis-(2,2,6,6-tetramethylpiperidin-4-yl)hexamethylenediamine, bis-(2,2,6,6-tetramethyl-piperidin-4-yl) sebacate, 2,2,6,6-tetramethylpiperidin-4-one or 2,2,6,6-tetramethyl-piperidin-4-ol; and

17) Aliphatic or aromatic phosphites, esters of thiodipropionic acid or of thiodiacetic acid, or salts of dithiocarbamic or dithiophosphoric acid, 2,2,12,12-tetramethyl-5,9-dihydroxy-3,7,1-trithiatridecane or 2,2,15,15-tetramethyl-5,12-dihydroxy-3,7,10,14-tetrathiahexadecane.

Examples of <u>metal passivators</u>, for example for copper, are:

1) Benzotriazoles and their derivatives, for example 4- or 5-alkylbenzotriazoles (e.g. tolutriazole) and derivatives thereof, 4,5,6,7-tetrahydrobenzotriazole, 5,5'-methylene-bisbenzotriazole; Mannich bases of benzotriazole or tolutriazole, such as 1-(di(2-ethylhexyl)aminomethyl)tolutriazole and 1-(di(2-ethylhexyl)aminomethyl)-benzotriazole; alkoxyalkylbenzotriazoles, such as 1-(nonyloxymethyl)-benzotriazole, 1-(1-butoxyethyl)-benzotriazole and 1-(1-cyclohexyloxybutyl)-tolutriazole;

2) 1,2,4-Triazoles and derivatives thereof, for example 3-alkyl(or aryl)-1,2,4-triazoles, Mannich bases of 1,2,4-triazoles such as 1-(di(2-ethylhexyl)aminomethyl)-1,2,4-triazole; alkoxyalkyl-1,2,4-triazoles such as 1-(1-butoxyethyl)-1,2,4-triazole; acylated 3-amino-1,2,4-triazoles;

3) Imidazole derivatives, for example 4,4'-methylenebis(2-undecyl-5-methyl-imidazole), bis((N-methyl)imidazol-2-yl)carbinol octyl ether;

4) Sulfur-containing heterocyclic compounds, for example 2-mercaptobenzothiazole, 2,5-dimercapto-1,3,4-thiadiazole, 2,5-dimercaptobenzothiadiazole and derivatives thereof; 3,5-bis(di(2-ethylhexyl)aminomethyl)-1,3,4-thiadiazolin-2-one; and

5) Amino compounds, for example salicylidenepropylenediamine, salicylaminoguanidine and salts thereof.

Examples of rust inhibitors are:

1) Organic acids, their esters, metal salts, amine salts and anhydrides, for example alkyl- and alkenylsuccinic acids and the partial esters thereof with alcohols, diols or hydroxycarboxylic acids, partial amides of alkyl- and alkenylsuccinic acids, 4-nonylphenoxyacetic acid, alkoxy- and alkoxyethoxycarboxylic acids, such as dodecyloxyacetic acid, dodecyloxy(ethoxy)acetic acid and the amine salts thereof, and also N-oleoylsarcosine, sorbitan monooleate, lead naphthenate, alkenylsuccinic anhydrides, for example dodecenylsuccinic anhydride, 2-(2-carboxyethyl)-1-dodecyl-3-methylglycerine and its salts, especially sodium and triethanolamine salts;

2) Nitrogen-containing compounds, for example primary, secondary or tertiary aliphatic or cycloaliphatic amines and amine salts of organic and inorganic acids, for example oil-soluble alkylammonium carboxylates, and also 1-(N,N-bis(2-hydroxyethyl)amino)-3-(4-nonylphenoxy)propan-2-ol; or heterocyclic compounds, for example: substituted imidazolines and oxazolines, 2-heptadecenyl-1-(2-hydroxyethyl)-imidazoline;

3) Phosphorus-containing compounds, for example amine salts of phosphoric acid partial esters or phosphonic acid partial esters, zinc dialkyldithiophosphates;

4) Sulfur-containing compounds, for example: barium dinonylnaphthalene-sulfonates, calcium petroleumsulfonates, alkylthio-substituted aliphatic carboxylic acids, esters of aliphatic 2-sulfocarboxylic acids and salts thereof; and

5) Glycerine derivatives, for example: glycerine monooleate, 1-(alkylphenoxy)-3-(2-hydroxyethyl)glycerines, 1-(alkylphenoxy)-3-(2,3-dihydroxypropyl)glycerines, 2-carboxyalkyl-1,3-dialkylglycerines.

Examples of viscosity index improvers are:

Polyacrylates, polymethacrylates, vinylpyrrolidone/methacrylate copolymers, polyvinylpyrrolidones, polybutenes, olefin copolymers, styrene/acrylate copolymers, polyethers.

Examples of pour point depressants are:

Polymethacrylates, alkylated naphthalene derivatives.

Examples of dispersants/surfactants are:

Polybutenylsuccinamides or -imides, polybutenylphosphonic acid derivatives, and basic magnesium, calcium and barium sulfonates, phenolates and salicylates.

Examples of antifoaming agents are: silicone oils and polymethocrylen.

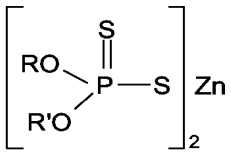
The demulsifiers are, for example, selected from:

Polyetherpolyols and dinonylnaphthalenesulfonates.

The friction modifiers are, for example, selected from:

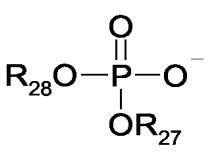
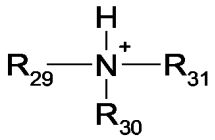
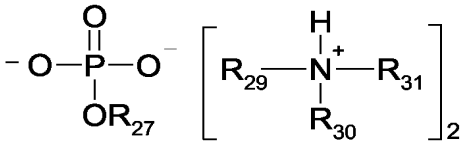
Fatty acids and their derivatives (i.e. natural esters of fatty acids such as glycerol monooleate), amides, imides and amines (i.e. oleylamine), sulfur containing organomolybdenum dithiocarbamates, sulfur-phosphorus containing organomolybdenum dithiophosphates, sulfur-nitrogen containing organomolybdenum compounds based on dispersants, molybdenum carboxylate salts, molybdenum-amine complexes, molybdenum amine/alcohol/amid complexes and molybdenum cluster compounds, Teflon® and molybdenum disulfide.
Examples of additional antiwear additives are:

- Sulfur- and/or phosphorus- and/or halogen-containing compounds, such as sulfurized olefins and vegetable oils, zinc dialkyldithiophosphates, tritolyl phosphate, tricresyl phosphate, chlorinated paraffins, alkyl and aryl di- and trisulfides, amine salts of mono- and dialkyl phosphates, amine salts of methylphosphonic acid, diethanolaminomethyltolyltriazole, di-(2-ethylhexyl)-aminomethyltolyltriazole, derivatives of 2,5-dimercapto-1,3,4-thiadiazole, ethyl(bisisopropyloxyphosphinothioyl)thiopropionate, triphenyl thiophosphate (triphenyl phosphorothioate), tris(alkylphenyl) phosphorothioates and mixtures thereof (for example tris(isononylphenyl) phosphorothioate), diphenylmonononylphenyl phosphorothioate, isobutylphenyl diphenyl phosphorothioate, the dodecylamine salt of 3-hydroxy-1,3-thiaphosphetan 3-oxide, trithiophosphoric acid 5,5,5-tris-isooctyl 2-acetate, derivatives of 2-mercaptobenzothiazole, such as 1-N,N-bis(2-ethylhexyl)aminomethyl-2-mercapto-1H-1,3-benzothiazole, and ethoxycarbonyl 5-octyldithiocarbamate;
- Dihydrocarbyl dithiophosphate metal salts where the metal is aluminum, lead, tin manganese, cobalt, nickel, zinc or copper, but most often zinc. The zinc salt (zinc dialkyl dithiophosphate) is represented as



where R and R' are independently C_1-C_{20} alkyl, C_3-C_{20} alkenyl, C_5-C_{12} cycloalkyl, C_7-C_{13} aralkyl or C_6-C_{10} aryl, for example R and R' are independently C_1-C_{12} alkyl;

- Antiwear additives as described in U.S. Patent Specification Nos. 4,584,021; 5,798,321; 5,750,478; 5,801,130; 4,191,666; 4,720,288; 4,025,288; 4,025,583 and in WO 095/20592, which are incorporated herein by reference; amines for example polyalkylene amines such as ethylene diamine, diethylene triamine, triethylene tetraamine, tetraethylene pentamine, pentaethylene hexamine, nonaethylene decamine and aryl amines as described in United States Patent Specification No. 4,267,063, herein incorporated by reference; salts of amine phosphates comprising specialty amines and mixed mono- and di-acid phosphates; the mono- and di-acid phosphate amines correspond to the structural formulae:



and

,

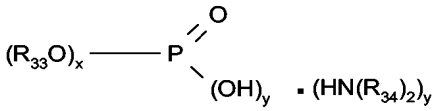
wherein R_{27} is hydrogen, C_1-C_{25} linear or branched chain alkyl which is unsubstituted or substituted by one or more C_1-C_6alkoxy groups, a saturated acyclic or alicyclic group, or aryl;

R_{28} is C_1-C_{25} linear or branched chain alkyl which is unsubstituted or substituted by one or more C_1-C_6alkoxy groups, a saturated acyclic or alicyclic group, or aryl;

R_{29} is hydrogen, C_1-C_{25} linear or branched chain alkyl, a saturated or unsaturated acyclic or alicyclic group, or aryl; and are hydrogen or C_1-C_{12} linear or branched chain alkyl; and

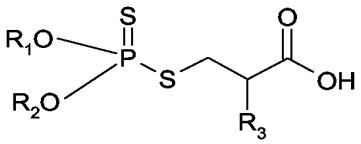
R_{30} and R_{31} are, each independently of the other, C_1-C_{25} linear or branched chain alkyl, a saturated or unsaturated acyclic or alicyclic group, or aryl. Preferably, R_{27} and R_{28} are linear or branched C_1-C_{12} alkyl; and R_{29}, R_{30} and R_{31} are linear or branched C_1-C_{18} alkyl;

- A mixture of amine phosphates, CAS# 80939-62-4, particularly by enhancing the wear performance of the base oil such that it meets stringent military performance specifications;



wherein R_{33} is n-hexyl, R_{34} is C_{11}-C_{14} branched alkyl, and when x=1 then y=2; when x=2 then y=1;

- Other conventional antiwear additives of the formula



in which R_1 and R_2 independently of one another are C_3-C_{18} alkyl, C_5-C_{12} cycloalkyl, C_5-C_6 cycloalkylmethyl, C_9-C_{10} bicycloalkylmethyl, C_9-C_{10} tricycloalkylmethyl, phenyl or C_7-C_{24} alkylphenyl or together are $(CH_3)_2C(CH_2)_2$,
R_3 is hydrogen or methyl.

The additives (I), (II), and (III) can be introduced into the lubricating oil in manners known per se. The compounds are readily soluble in oils. They may be added directly to the lubricating oil or they can be diluted with a substantially inert, normally liquid organic diluent such as naphtha, benzene, toluene, xylene or a normally liquid oil to form an additive concentrate or masterbatch. These concentrates generally contain from about 10% to about 90% by weight additive and may contain one or more other additional additives. The additives may be introduced as part of an additive package.

A further embodiment of the invention relates to process for the reduction of wear in combustion engines, which comprises adding to the engine the lubricant composition as defined above. In a preferred embodiment the total amount of sulphur in that composition is less than 0.3%, particularly 0.2%, by weight and that of phosphorus less than 0.08% by weight.

The invention is further illustrated by the following Examples. Unless otherwise indicated, parts and percentages are by weight.

Example 1

Preparation of Ethylenediamine tetra-N-n-octylacetamide

To a stirred mixture of 2.80 g ethylenediamine, 20.06 g sodium carbonate, and 100 mg potassium iodide in 100 ml acetonitrile is added a solution of 38.35 g of 2-chloro-N-n-octylacetamide. After being stirred at ambient temperature for 18 hours, the mixture is heated at reflux for 5 days. After cooling, the mixture is partitioned between 400 ml dichloromethane and 250 ml water. The aqueous phase is further extracted with 200 ml dichloromethane. The

combined organic extract is washed with water (200 ml), brine (200 ml) and dried over anhydrous sodium sulfate. The solvent removed *in vacuo*, and the resulting residue is recrystallized from ethyl acetate to give the product as a pale yellow fibrous wax.

Example 2

Preparation of Ethylenediamine tetra-N,N-di-n-octylacetamide

A mixture of 78.7 g 2-chloro-N,N-dioctylacetamide, 3.7 g ethylenediamine and 26.2 g sodium carbonate in 300 ml N,N-dimethylacetamide is heated at 90°C for 3 hours and at 120°C for another 16 hours. The mixture is cooled, washed with water, extracted with hexane and dried over sodium sulfate. The hexanes are removed *in vacuo* to give 74.9 g of product as a viscous yellow liquid.

Alternative one-pot procedure:

To a rapidly stirred mixture of di-n-octylamine (25.03 g), xylene (25 ml), Na_2CO_3 (12.5 g) and water (125 ml) chloroacetyl chloride (12.4 g) is added dropwise over 20 min. Intermittent cooling is applied to maintain temperature between 20–25°C. After completion of addition, the mixture is stirred for 30 min. The phases are allowed to separate, and the lower aqueous phase is removed. N,N-Dimethylacetamide (25 ml), ethylenediamine (1.55 g), and Na_2CO_3 (12.5 g) are added, and the mixture heated with stirring to 120°C. The reaction mixture is heated for 18 hrs, allowed to cool and mixed with water (125 ml) to dissolve salts and DMAc. After removing the aqueous phase the solvents are removed *in vacuo*. The product is filtered to remove sediments, to yield 28.77 g (93%) of product as a pale, yellow oil. Xylene may be replaced with other suitable solvents, for example ethylbenzene.

Example 3

Preparation of N,N-di-n-octyl-2-(di-n-octylamino)acetamide

To a rapidly stirred solution 32.62 g di-n-octylamine in 100 ml acetonitrile, 7.62 g 2-chloroacetyl chloride is added over a 1 hour period. The mixture is stirred at ambient temperature for 3 hours, followed by the addition of 15.91 g sodium carbonate and 0.63 g potassium iodide. The mixture is heated at reflux for 24 hours. After cooling, the mixture is partitioned between 250 ml dichloromethane and 250 ml water. The aqueous phase is further extracted with 250 ml dichloromethane. The combined organic extract is washed with water (100 ml), brine (100 ml) and dried over anhydrous sodium sulfate. The solvent is removed in vacuo and the resulting residue is partitioned between hexane (300 ml) and acetonitrile (250 ml). After filtering to remove undissolved solids, the phases are separated, and the yel-

low hexanes phase is washed with 2 portions (100 ml each) acetonitrile. The solvent is removed *in vacuo* to give the product as a waxy orange oil.

Example 4

Preparation of Diethylenetriamine penta-N,N-di-n-octylacetamide

A mixture of 31.8 g 2-chloro-N,N-dioctylacetamide, 2.08 g diethylenetriamine and 10.6 g sodium carbonate in 150 ml N,N-dimethylacetamide is heated at 150°C for 48 hours. After cooling the mixture is washed with water, extracted with hexane and dried over sodium sulfate. The hexane is removed *in vacuo* to give 30.6 g of the product as a dark brown liquid.

Example 5

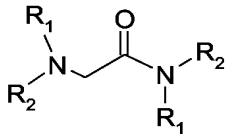
Preparation of Ethylenediamine tetra-N-oleylacetamide

To a rapidly stirred mixture of oleylamine (118.5 g), diether (200 ml), Na_2CO_3 (50.29 g) and water (500 ml) 2-chloroacetyl chloride (54.16 g) is added dropwise over 60 min. Intermittent cooling is applied to maintain temperature between 10-15°C. After completion of addition, the mixture is stirred for 60 min, and the phases are allowed to separate. Analysis (H-NMR) of a sample of the upper ether layer indicates that a small amount of amine is not reacted. Additional Na_2CO_3 (7 g) and water (50 ml) is added, followed by chloroacetyl chloride (7 g). After removing the upper ether phase the aqueous phase is extracted with additional ether (200 ml). The combined organic phase is washed with water (2 x 125 ml portions), saturated NaCl (125 ml) and dried over anh. Na_2SO_4. The solvent is removed *in vacuo* to give 149 g 2-chloro-N-oleylacetamide.

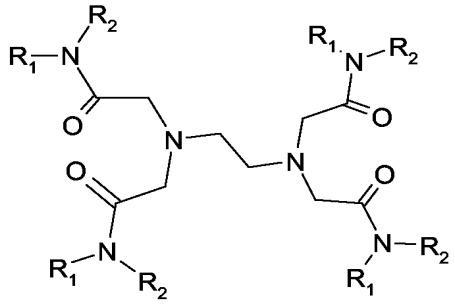
A mixture of ethylenediamine (1.01 g), 2-chloro-N-oleylacetamide (23.13 g), N,N-dimethylacetamide (50 ml) and Na_2CO_3 (25.8 g) is heated for 20 hours at 120-130°C. After cooling, the reaction mixture is partitioned between diethyl ether (250 ml) and water (250 ml). The ether layer is washed with water (3 x 100 ml), saturated NaCl (100 ml) and dried over anh. Na_2SO_4. The solvent is removed *in vacuo* to give 20.4 g of the tetra-alkylated product.

Example 6

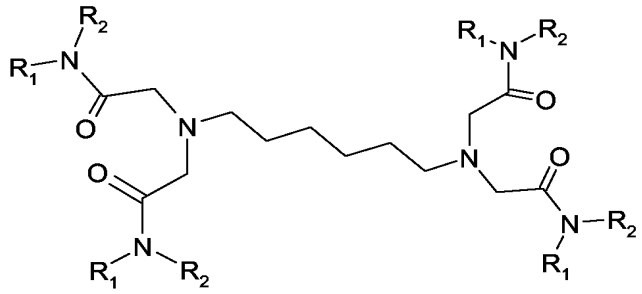
The following compounds are prepared according to the methods described herein.



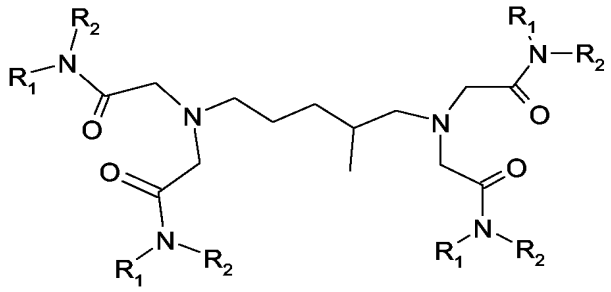
R_1	R_2	Physical Form
n-Octyl	n-Octyl	Liquid (Ex.3)



R_1	R_2	Physical Form
2-Ethylhexyl	2-Ethylhexyl	Liquid
n-Octyl	n-Octyl	Liquid (Ex. 29
Oleyl	Hydrogen	Wax (Ex. 5)
n-Octyl	Hydrogen	Wax (Ex. 1)
t-Octyl	Hydrogen	Solid
Dodecyl	Hydrogen	Solid
C_{12}-C_{15}Alkyl	Hydrogen	Syrup
C_{18}-C_{24}Alkyl	Hydrogen	Syrup



R_1	R_2	Physical Form
n-Octyl	n-Octyl	Liquid
t-Octyl	Hydrogen	Resin
2-Ethylhexyl	2-Ethylhexyl	Liquid



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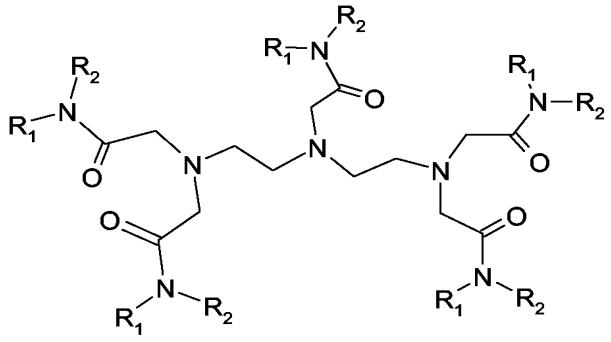
R_1	R_2	Physical Form
t-Octyl	Hydrogen	Resin



R_1	R_2	Physical Form
n-Octyl	n-Octyl	Liquid (Ex. 4)
2-Ethylhexyl	2-Ethylhexyl	Liquid

Example 7

Application Example

Antiwear properties are measured on a PCS Instruments Mini-Traction Machine, modified with a Pin-on-Disc attachment, in which a stationary pin (500 x 500 μ) is held against a rotating disc. A fixed load is applied at a constant temperature. Wear is measured as the displacement of the pin, due to loss of material from the pin. The test oil is a zero S, very low P automotive engine oil, fully formulated except that no antiwear additive is included. The reaction test conditions are 10N load, oil temperature 100°C. Wear data is recorded for 60 min, and the average wear rate is reported here as the linear regression slope of the wear curve.

Oil	Wear Rate
Test oil (no antiwear additive)	279 μ/hr
Test oil + 1.2% ZDDP	3.0 μ/hr
Test oil + 1% additive of Example 2	16 μ/hr

ZDDP is zinc dialkyl dithiophosphate. A secondary ZDDP at 1.2% provides 0.1% P.

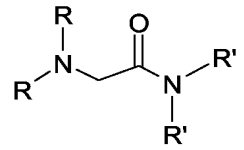
Claims

1. A composition, which comprises

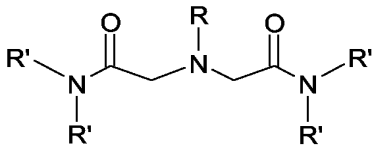
c) A base oil of lubricating viscosity; and

d) An effective antiwear or friction modifying amount of at least one compound selected from the group consisting of

N-alkylaminoacetamide compounds (I), (II):

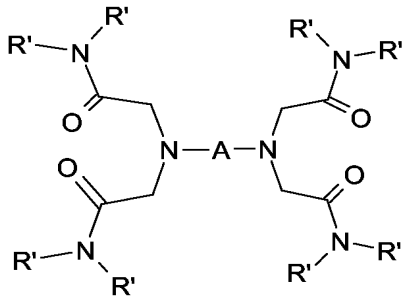


(I),



(II) and

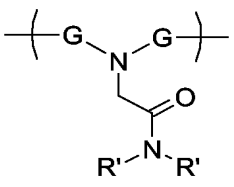
Alkylenedi-, alkylenetri- or alkylenetetra-amine acetamide compounds (III):



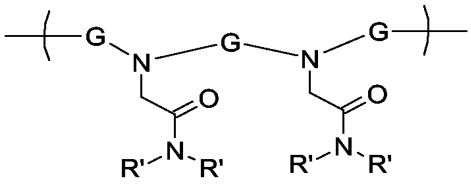
(III),

Wherein

A is alkylene of from 2 to 6 carbon atoms or is a group



or



,

G, each independently, is alkylene of 2 to 6 carbon atoms,

R, each independently, is alkyl or alkenyl of 1 to 8 carbon atoms and

R', each independently, is hydrogen or alkyl or alkenyl or 1 to 24 carbon atoms,

provided that

each amide nitrogen atom is either mono- or disubstituted by alkyl or alkenyl; and that the alkyl or alkenyl groups have 8 to 24 carbon atoms, if the amide nitrogen is monosubstituted by alkyl or alkenyl; and

that the carbon atoms of the alkyl or alkenyl groups have 8 to 18 carbon atoms, if the amide nitrogen is disubstituted by alkyl or alkenyl.

2. A composition according to claim 1, which comprises at least one compound selected from the group consisting of N-alkylaminoacetamide compounds (I) and (II), wherein the total number of carbon atoms of the alkyl or alkenyl groups are from 14 to 18 carbon atoms if the amide nitrogen is disubstituted by alkyl or alkenyl.

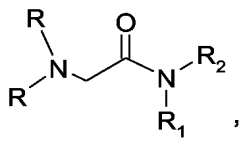
3. A composition according to claim 1, which comprises at least one compound selected from the group consisting of alkylenedi-, alkylenetri- and alkylenetetra-amine acetamide compounds (III), wherein A and G are selected from the group consisting of ethylene, propylene, hexamethylene and 2-methylpentylene.

4. A composition according to claim 1, wherein each R' is independently straight or branched chain alkyl or alkenyl of 7 to 9 carbon atoms.

5. A composition according to claim 1, wherein one R' is hydrogen and the other one is straight or branched chain alkyl or alkenyl of 14 to 18 carbon atoms.

6. A composition according to claim 1, wherein each R' is identical and is straight or branched chain alkyl or alkenyl of 7 to 9 carbon atoms.

7. A composition according to claim 1, wherein the compounds (I), (II) and (III) are selected from the group consisting of



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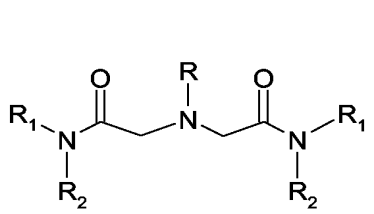
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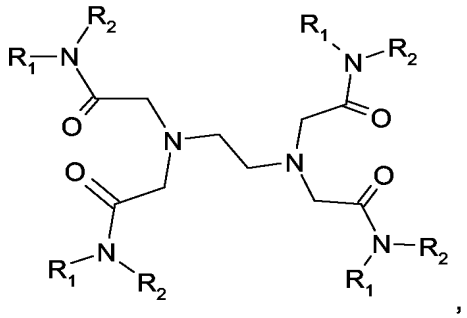
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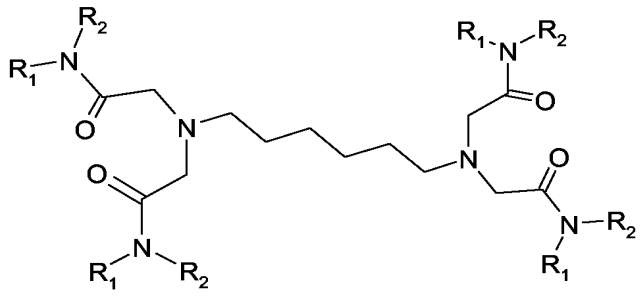
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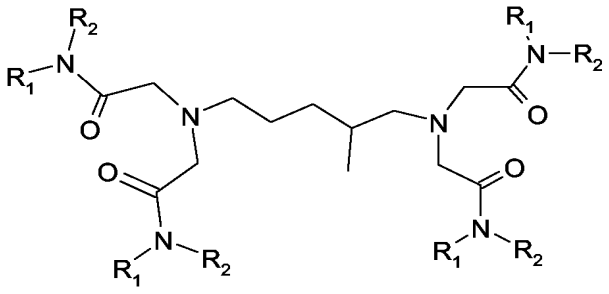
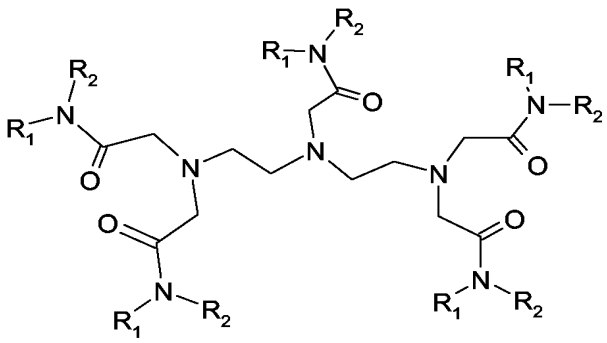
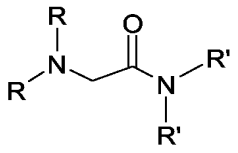

and


wherein R is n-octyl and each of R_1 and R_2 are 2-ethylhexyl or n-octyl or one of R_1 and R_2 is hydrogen and the other is oleyl, n-octyl, t-octyl or dodecyl.

8. An alkylaminoacetamide compound (I)



(I)

,

Wherein

R, each independently, is alkyl or alkenyl of 1 to 8 carbon atoms and

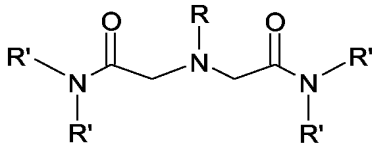
R', each independently, is hydrogen or alkyl or alkenyl or 1 to 24 carbon atoms,

provided that

each amide nitrogen atom is either mono- or disubstituted by alkyl or alkenyl; and that the alkyl or alkenyl groups have 8 to 24 carbon atoms, if the amide nitrogen is mono-substituted by alkyl or alkenyl; and

that the alkyl or alkenyl groups have 8 to 18 carbon atoms, if the amide nitrogen is disubstituted by alkyl or alkenyl.

9. An N-alkylaminoacetamide compound (II)



(II)

,

Wherein

R, each independently, is alkyl or alkenyl of 1 to 8 carbon atoms and

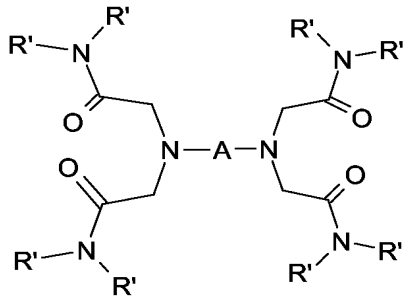
R', each independently, is hydrogen or alkyl or alkenyl or 1 to 24 carbon atoms,

provided that

each amide nitrogen atom is either mono- or disubstituted by alkyl or alkenyl; and that the alkyl or alkenyl groups have 8 to 24 carbon atoms, if the amide nitrogen is mono-substituted by alkyl or alkenyl; and

that the alkyl or alkenyl groups have 8 to 18 carbon atoms, if the amide nitrogen is disubstituted by alkyl or alkenyl.

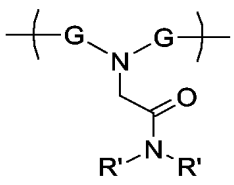
10. An alkylenedi-, alkylenetri- or alkylenetetra-amine acetamide compound (III)



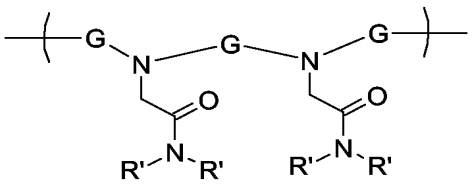
(III)

wherein

A is alkylene of from 2 to 6 carbon atoms or is a group



or



,

G, each independently, is alkylene of 2 to 6 carbon atoms,

R', each independently, is alkyl or alkenyl of 1 to 24 carbon atoms, where for each amide group, the total number of carbon atoms of the alkyls or alkenyl groups are from 14 to 18 carbon atoms.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/054347

A. CLASSIFICATION OF SUBJECT MATTER
C10M133/16 C07C237/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C10M C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2 191 978 A (BALLE GERHARD ET AL) 27 February 1940 (1940-02-27) column 1, line 1 - line 40 claims; examples 4,5	8
X	US 2 516 674 A (BRUCE WILLIAM F ET AL) 25 July 1950 (1950-07-25) column 1, line 4 - line 11 claims; examples	8
X	US 2 548 863 A (BRUCE WILLIAM F ET AL) 17 April 1951 (1951-04-17) column 1, line 24 - line 55 claims	8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 November 2005	25/11/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Dötterl, E

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/054347

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 358 387 A (ZOLESKI ET AL) 9 November 1982 (1982-11-09) column 1, line 40 - line 43 column 2, line 60 - column 3, line 14 claims; examples	1-10
A	US 2 411 662 A (MARTIN HENRY ET AL) 26 November 1946 (1946-11-26) the whole document	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/054347

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2191978 A	27-02-1940	NONE	
US 2516674 A	25-07-1950	NONE	
US 2548863 A	17-04-1951	NONE	
US 4358387 A	09-11-1982	NONE	
US 2411662 A	26-11-1946	NONE	